Current Psychiatry Reports (2019) 21: 124
https://doi.org/10.1007/s11920-019-1114-0

SCHIZOPHRENIA AND OTHER PSYCHIATRIC DISORDERS (AK PANDURANGI, SECTION EDITOR)

Long-Acting Injections in Schizophrenia: a 3-Year Update on Randomized Controlled Trials Published January 2016–March 2019

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Published online: 19 November 2019

Abstract

Purpose of Review This study was conducted in order to review randomized controlled trial (RCT) data published January 2016–March 2019 on long-acting injectable antipsychotics (LAIs) for schizophrenia.

Recent Findings Thirty-one RCTs (primary studies = 7; post hoc analyses = 24; $n = 4738$) compared LAIs vs. placebo (studies = 11, $n = 1875$), LAIs vs. oral antipsychotics (OAPs) (studies = 7, $n = 658$), and LAI vs. LAI (studies = 13, $n = 2205$). LAIs included two new formulations, aripiprazole lauroxil nanocrystal dispersion and subcutaneously injectable risperidone Perseris, as well as aripiprazole lauroxil, aripiprazole once-monthly, paliperidone once-monthly, paliperidone 3-monthly, and risperidone-LAI. Regarding prevention of relapse and hospitalization, LAIs consistently outperformed placebo, being partly superior to OAPs, without relevant LAI–LAI differences. LAIs were comparable to OAPs regarding all-cause discontinuation, functioning, quality of life, and tolerability, being associated with higher patient satisfaction and service engagement. Recent meta-analyses yielded mixed results, but never favoring OAPs over LAIs.

Summary In RCTs, LAIs are superior to placebo, but only in some aspects, superior to OAPs. Comparative effectiveness of LAIs vs. OAPs requires further study, ideally in generalizable/real-world samples.

Keywords Schizophrenia · Antipsychotics · Long-acting injectables · Relapse · Hospitalization · Symptom improvement · Acceptability · Discontinuation · Meta-analyses

Introduction

Schizophrenia remains one of the most severe medical diseases [1]. The treatment of this chronic and often disabling disorder has come a long way with the initial development of antipsychotics and atypical antipsychotics [2–5], which have remained the only approved and effective pharmacologic treatment for schizophrenia [4, 6•]. Despite pharmacologic advances in recent years, an

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This article is part of the Topical Collection on *Schizophrenia and Other Psychiatric Disorders*

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effective treatment of schizophrenia remains an issue, both due to insufficient treatment of cognition and negative symptoms as well as the challenge of treatment nonadherence, which is strongly linked to recurrent relapses [7, 8]. Given the need for long-term maintenance treatment in schizophrenia [9•], relapse prevention is a major goal [10, 11•, 12].

In order to improve adherence to prescribed antipsychotics through less frequent dosing schedules and readily observable nonadherence, long-acting injectable antipsychotics (LAIs) have been developed [13••]. Although in randomized controlled trials that systematically include more adherent patients who know that their medication adherence will be monitored closely [14], LAIs were not superior to oral antipsychotics (OAPs) regarding relapse and treatment continuation [15], and meta-analyses of mirror image and cohort studies that arguably enroll more generalizable patients [14] demonstrated that LAIs are superior to OAPs in treatment discontinuation [16, 17•], relapse [18] and hospitalization [16, 17], time to relapse [18], and hospital days [18]. As schizophrenia is often associated with functional impairments, recent research also focused on the maintenance and improvement of functionality and quality of life with both oral antipsychotics [19•] and LAIs [13]. In terms of tolerability and safety, meta-analyses have demonstrated that LAIs are comparable to OAPs [20•, 21•], with one meta-analysis favoring LAIs over OAPs [18].

Furthermore, novel long-acting injectable formulations have emerged, aiming to move from deep intramuscular to subcutaneous injections and/or abolish the need for initial oral cotreatment or loading injection strategies, which may increase acceptability [6]. These formulations include RBP-7000 (Perseris™), a long-acting injectable formulation of risperidone [22], requiring no oral supplementation and being the first antipsychotic available as a subcutaneously (intraabdominally) administered LAI [23•], and aripiprazole lauroxil nanocrystal dispersion (AL_{NCD}; Aristada Initio™), a 1-day initiation regimen for the LAI aripiprazole lauroxil (AL), reducing oral supplementation to the first day of administration and enabling faster release of aripiprazole into plasma [24].

Despite demonstrated advantages of LAIs, they remain largely underutilized in clinical practice, possibly due to lack of familiarity of many physicians, incomplete or inaccurate perceptions about safety and efficacy, medication cost considered in isolation without taking into account overall reductions in cost of care due to reduced relapse and hospitalizations, issues with access to treatment, and negative perceptions about injectable therapy among patients, families, and prescribers [13].

In this context, this systematic review aimed to summarize evidence from articles published 2016–2019 that reported data on findings of randomized controlled trials (RCTs) regarding (i) new long-acting injectable formulations; (ii) the efficacy of LAIs for symptom improvement and prevention of relapse and hospitalization, functionality, and quality of life; (iii) the tolerability and safety of LAIs; and (iv) attitudes toward and acceptability of LAIs. Since a comprehensive review of the literature on the use of LAIs up to 2015 already exists [13], we focused on the time frame 2016–2019.

Methods

We aimed to summarize the recent evidence of RCTs comparing LAIs to placebo, OAPs, or another LAI for schizophrenia-spectrum disorders. Therefore, we conducted a systematic literature search of articles published in PubMed between 01 January 2016 and 26 March 2019, using the following search terms: ((schizophrenia OR schizophreniform OR schizoaffective OR psychosis OR psychotic) AND (depot OR long-acting injectable OR injection* OR microsphere* OR decanoate OR palmitate OR enanthate OR monohydrate OR lauroxil OR nanocrystal)).

We included RCTs that investigated LAIs in adults with schizophrenia-spectrum disorders focusing on new LAI formulations (AL_{NCD} and RBP-7000), efficacy of LAIs for symptom improvement and prevention of relapse and hospitalization, functionality and quality of life, tolerability and safety of LAIs, and attitudes toward as well as acceptability of LAIs. Additionally, we considered published expert recommendations for the use of LAIs. We excluded studies in children and adolescents, reporting on mixed-age populations without reporting results separately for adults, and LAI dose comparisons. Finally, we also reviewed meta-analytic results of RCTs, as long as the meta-analysis was published in January 2016 or later.

Results are summarized first for the individual RCTs focusing on the following five characteristics/outcomes: [1] FDA approval trial, [2] efficacy for symptom improvement and prevention of relapse/hospitalization, [3] efficacy for functionality/quality of life, [4] tolerability/safety, and [5] attitudes/acceptability, dividing the results by the comparator (placebo, OAP, LAI). At the end, results of the meta-analyses are summarized for efficacy and safety/tolerability of LAIs vs. the meta-analyzed comparator.

Results

Search Results and Study Characteristics

The PubMed search resulted in 821 hits. After removal of 776 articles based on title and abstract review, 45 full text articles were inspected for eligibility. Of these, 14 were excluded for the following reasons: LAI dose comparison (n = 8), short-acting injectable data (n = 4), no data on LAIs (n = 1), and duplicate publication (n = 1). Ultimately, we included 31 RCTs (primary data studies: k = 7; post hoc analyses: k = 24; individual patients: n = 4738), comparing LAIs vs.

placebo (studies = 11, n = 1875) and LAIs vs. OAPs (studies = 7, n = 658) and comparing one LAI vs. another LAI (studies = 13, n = 2205). Altogether, 20 studies (n = 3812) had a double-blind (DB) and 11 had a randomized, open-label (ROL) (n = 926) design.

Additionally, five meta-analyses of RCTs of LAIs in schizophrenia [18, 20•, 21•, 25, 26] were identified, with all five focusing on LAI vs. OAP comparisons and one of them also including placebo-controlled trials [26]. Three meta-analyses focused on efficacy, effectiveness, and tolerability outcomes (1. RCTs = 17, n = 6362; 2. RCTs = 1, n = 4796; 3. RCT = 5, n = 1022) [18, 20•, 25], and two focused on safety/tolerability outcomes only (1. RCTs = 16, n = 4902; 2. RCTs = 52, n = 17,416, LAI: n = 11,360, OAP: n = 3910, placebo: n = 2146) [21•, 26].

New LAI Formulations (AL_{NCD} and RBP-7000)

Between 2016 and 2019, four LAI studies (placebo-controlled: k = 3, OAP-controlled: k = 0, LAI–LAI comparisons: k = 1), one being a post hoc analysis of a previously published primary study, investigated new and recently approved LAI formulations in patients with schizophrenia-spectrum disorders.

Aripiprazole Lauroxil NanoCrystal Dispersion Vs. Aripiprazole Lauroxil In a 6-month, double-blind placebo-controlled trial (DBPCT) (industry sponsor: Alkermes) in 161 patients with stable but symptomatic schizophrenia who were randomly assigned to one of four treatments with the 1-day initiation regimen (AL_{NCD} + AL 441-mg + 30-mg oral aripiprazole on day 1 [n = 39] or AL_{NCD} + AL 882-mg + 30-mg oral aripiprazole on day 1 [n = 31]) or the previously approved 21-day regimen (AL 441-mg + 15-mg oral aripiprazole + 20 days 15-mg oral aripiprazole [n = 40], or AL 882-mg, 15-mg oral aripiprazole + 20 days 15-mg oral aripiprazole [n = 41]), $AUC_{0–28}$ values (mean ± SD) were comparable in each treatment group: AL 441 mg/1-day initiation regimen, 1222.4 (455.7) ng/mL; AL 882 mg/1-day initiation regimen, 1126.6 (597.4) ng/mL; AL 441 mg/21-day initiation regimen, 1435.5 (654.8) ng/mL; and AL 882 mg/21-day initiation regimen, 1315.9 (439.6) ng/mL [27]. All groups achieved aripiprazole concentrations in the therapeutic range within 4 days and remained in a comparable concentration range during treatment initiation [27] (Table 1).

Risperidone Perseris Vs. Placebo In an 8-week, DBPCT (industry sponsor: Indivior) in 337 patients with acute schizophrenia who were randomly assigned to RBP-7000 90 mg (n = 111), RBP-7000 120 mg (n = 114), or placebo (n = 112), both doses of RBP-7000 significantly improved Positive and Negative Symptom Scale (PANSS) total (90 mg: p = 0.0004; 120 mg: p < 0.0001) and Clinical and Global Impression Scale-Severity (CGI-S) scores (90 mg: p = 0.0002; 120 mg: p < 0.0001) vs. placebo [28•] (Table 1). In a post hoc analysis of the same study [28•], the maximum placebo-corrected relative decrease in PANSS score in the RBP-7000 group was 5.4%, half of which was achieved at plasma concentrations of 4.6 ng/mL of the total active moiety [29] (Table 1). Furthermore, favorable results were found for RBP-7000 in terms of functioning, quality of life, and satisfaction with preference for medication compared to placebo [53] (see sections "Efficacy of LAIs for Functional Outcomes and Quality of Life" and "All-Cause Discontinuation and Attitudes Toward and Acceptability of LAIs").

Efficacy of LAIs for Symptom Improvement and Prevention of Relapse and Hospitalization

Sixteen studies of LAIs (placebo-controlled: k = 5, OAP-controlled: k = 7; LAI–LAI comparisons: k = 5), of which 13 were post hoc analyses of previously published studies, reported on symptom improvement and prevention of relapse and hospitalization in patients with schizophrenia-spectrum disorders. Symptomatic efficacy results are summarized by individual LAI and specific study comparator in Table 1. Specific results (not only for subgroups or for time to event) regarding relapse (studies = 3) [37, 44, 49] and hospitalization rates (studies = 2) [43, 44] are summarized by individual LAI and specific study comparator in Table 2 and Fig. 1.

Placebo-Controlled Trials of LAIs

Aripiprazole Once-Monthly 400 mg Vs. Placebo In a post hoc analysis of a 12-week, DBPCT (industry sponsor: Otsuka and Lundbeck) in 329 patients with acute schizophrenia that compared aripiprazole once-monthly (AOM) 400 mg (n = 162) with placebo (n = 167) every 4 weeks [31], AOM showed significantly greater efficacy vs. placebo in all five PANSS Marder factor scores (p < 0.0001) (positive symptoms, negative symptoms, disorganized thought, uncontrolled hostility/excitement, and anxiety/depression) and in agitation as measured by the PANSS excited component score (each p < 0.0001) [30] (Table 1).

Aripiprazole Lauroxil Vs. Placebo In a post hoc analysis of a 12-week, DBPCT (industry sponsor: Alkermes) in 623 patients with acute schizophrenia, comparing AL 441 mg (n = 207), AL 882 mg (n = 208), and placebo (n = 208) [33], both AL doses were superior to placebo on the PANSS subscale, PANSS Marder factors, and CGI-S scores (all p < 0.001) [32]. Moreover, overall response (≥ 30% decrease in PANSS total score or a CGI-I score of 1 or 2) was significantly greater with both doses of AL (882 mg—56%, p = 0.001; 441 mg—52%, p = 0.001) vs. placebo (28%) [32] (Table 1).

Table 1 Randomized controlled trials of long-acting injectable antipsychotics: symptomatic efficacy

Reference/design/country	Total *N*	Duration (weeks)	Population	Outcome	Age (years)	% Male	% Hp at BL	Illness duration/age of onset	LAI/comparator	*N* per arm	Dose (mg)	Symptomatic efficacy
RBP-7000 vs. PBO *k* = 1, *n* = 337, age = 41.2, male = 77.5%												
Nasser et al., 2016 [28•]/DBPCT/Ivaturi et al., 2017 [29]/post hoc analysis/USA	337	8	Acutely exacerbated SCZ w/ PANSS total of 80–120	*PANSS total*, CGI-S Post hoc: *Total AM plasma exposure*, PANSS total, CGI-S	41.2	76.5	N/Av	N/Av	RBP-7000 PBO	111 114 112	90 120	RBP-7000 significantly improved PANSS total scores (90 mg $p = 0.0004$; 120 mg $p < 0.0001$) and CGI-S scores (90 mg $p = 0.0002$; 120 mg $p < 0.0001$) Post hoc: the max. PBO-corrected relative decrease in PANSS total score following RBP-7000 tx was 5.4%, half of which could be achieved at plasma concentrations of 4.6 ng/mL of the total AM
AL_{NCD} vs. AL *k* = 1, *n* = 161, age = 44.0, male = 73.3%												
Hard et al., 2018 [27]/DBPCT/USA	161	24	Clinically stable SCZ or SAD	*Mean plasma concentrations*	44.0	73.3	0	N/Av	AL, oral ARI, AL_{NCD}, + 20 days oral PBO AL, oral ARI, PBO, + 20 days oral ARI	39 and 41 40 and 41	441 or 882 + 30 441 or 882 + 15	Comparable AUC_{0-28} values (mean ± SD): AL 441-mg/1-day initiation regimen, 1222.4 (455.7) ng/mL; AL 882-mg/1-day initiation regimen, 1126.6 (597.4) ng/mL; AL 441--mg/21-day initiation regimen, 1435.5 (654.8) ng/mL; AL 882-mg/21-day initiation regimen, 1315.9 (439.6) ng/mL
AOM vs. PBO *k* = 1, *n* = 329, age = 42.4, male = 79.1%												
Ismail et al., 2017 [30]/post hoc analysis of DBPCT [Kane et al., 2014 [31]]/USA	329	12	Acutely exacerbated SCZ w/ PANSS total score ≥ 80	*PANSS Marder factor domains*, PANSS excited component	42.4	79.1	100	N/Av	AOM PBO	162 167	400	AOM showed significantlygreater efficacy vs. PBO in all 5 PANSS Marder factor scores ($p < 0.0001$) and in the PANSS exited component ($p < 0.0001$)
AL vs. PBO *k* = 2, *n* = 932, age = 39.7, male = 68.3%												
Citrome et al., 2018 [32]/post hoc analysis of DBPCT [Meltzer et al., 2015 [33]]/USA, Ukraine, Russia, Bulgaria, Romania, Philippines, Malaysia	623 (596 analyzed)	12	Acutely exacerbated SCZ w/ PANSS total score of 70–120	*PANSS subscales*, *PANSS Marder factors*, *CGI-S*, Treatment response (CGI-I, PANSS total)	39.7	67.9	100	N/Av	AL PBO	207 208 208	441 882	PANSS subscale, PANSS Marder factor, and CGI-S scores were significantly ($p < 0.001$) improved w/ both doses of AL vs. PBO. Treatment response rates were significantly ($p < 0.001$) greater w/ AL (882 mg 56%, $p = 0.001$, 441 mg 52%, $p = 0.001$) vs. PBO (28%)

Table 1 (continued)

Reference/design/country	Total *N*	Duration (weeks)	Population	Outcome	Age (years)	% Male	% Hp at BL	Illness duration/age of onset	LAI/comparator	*N* per arm	Dose (mg)	Symptomatic efficacy
Potkin et al., 2017 [34]/post hoc, subgroup analysis of DBPCT [Meltzer et al., 2015 [33]]/USA, Ukraine, Russia, Bulgaria, Romania, Philippines, Malaysia	309 (294 analyzed)	12	Acutely exacerbated SCZ w/ PANSS total above the median score of 92	*PANSS total*, PANSS subscales	39.7	69.0	100	N/Av	AL PBO	100 104 105	441 882	Sig. improvement in PANSS total: PBO-adjusted differences were − 14.7 ($p < 0.0001$) for AL 441 mg and − 16.6 for AL 882 mg. Sig. improvement in PANSS subscales for both doses ($p < 0.0001$–$p < 0.0035$). Significantly higher responder rates w/AL (441 mg 49%, $p < 0.001$, 882 mg 61%, $p < 0.001$) vs. PBO (18%)
PP1M vs. PBO $k = 1$, $n = 133$, age = 39.4, male = 54.1%												
Emsley et al., 2018 [35]/post hoc and subgroup analysis of DBPCT [Hough et al., 2010 [36]]/South Africa	133	Stabilization on PP1M 9, DBPCT 96	Relapsed SCZ patients	*PANSS total*, PANSS domains	39.4	54.1	N/Av	100% ≥ 1 year	PP1M PBO	97 36	25, 50 or 100	No sig. difference in PANSS total ($p = 0.9$) and domain scores ($p = 0.62$–$p = 0.95$)
PP3M vs. PBO $k = 1$, $n = 119$, age = 31.5, male = 72.3%												
Bell Lynum et al., 2018 [37]/post hoc analysis of DBPCT [Berwaerts et al., 2015 [38]]/Ukraine, USA, Romania, Colombia, Malaysia, Mexico, Turkey, South Korea	119	Stabilization on PP1M 17 DBPCT up to 2 years	Early illness SCZ (≤ 5 years) w/ PANSS total score < 120	*Time to relapse*, PANSS total, PANSS subscales, CGI-S	31.5	72.3	N/Av	100% ≤ 5 years	PP3M PBO	62 57	175, 263, 350, or 525	PP3M was superior to PBO in time to relapse ($p = 0.035$; HR, 3.08; 95% CI, 1.08–8.80) and PANSS total ($p = 0.003$), positive ($p = 0.011$), negative ($p = 0.019$), and general ($p = 0.006$) subscale, and CGI-S ($p = 0.025$) scores
PP1M vs. OAP $k = 2$, $n = 444$, age = 38.2, male = 86.2%												
Alphs et al., 2016 [39], Alphs et al., 2018 [40] and Starr et al., 2018 [41]/post hoc analyses of ROLT [Alphs et al., 2014 [42]]/USA	444	60	SCZ, taken into custody by the CJS ≥ 2 times in the previous 2 years w/ ≥ 1 leading to incarceration	*Mean number of tx failures (measured by MCF)*; *Time to first tx failure (analysis based on age of onset)*; *Time to first tx failure (analysis based on comorbid SA)*	38.2	86.3	N/Av	N/Av	PP1M OAPs: ARI, HAL, OLAN, PALI, PER, QUE, RIS	226 (130 w/ SA, 96 w/o SA, 42 ≤ 5 years, 183 > 5 years) 218 (134 w/ SA, 84 w/o SA, 35 ≤ 5 years, 182 > 5 years)	78–234 variable	The MCF of tx failures ($p = 0.007$) and institutionalizations ($p = 0.005$) differed significantly in favor of PP1M vs. OAPs. Median time to first tx failure: Recent-onset: PP > 450 days; OAPs 270 days; chronic illness: PP 416 days, OAPs 210 days; w/ SA: PP 291 days, OAPs 186 days; w/o SA: PP > 450 days, OAPs 284 days
Kim et al., 2016 [43]/post hoc analysis of ROLT [Alphs et al., 2014	171 407 293	60	SCZ, taken into custody by the CJS ≥ 2 times in the previous 2	*Time to first tx failure*	36.9 38.2 37.7	87.2 86.0 84.6	77% 79% 78%	22% ≤ 5 years 78% > 5 years 17% ≤ 5 years	PP1M COAP (HAL, PER) PP1M	136 35 224	78–234 variable 78–234	Median number of days to tx failure:

Table 1 (continued)

Reference/design/country	Total *N*	Duration (weeks)	Population	Outcome	Age (years)	% Male	% Hp at BL	Illness duration/age of onset	LAI/comparator	*N* per arm	Dose (mg)	Symptomatic efficacy
[42]]/USA			years w/ ≥ 1 leading to incarceration					83% > 5 years 18% ≤ 5 years 82% > 5 years	AOAP (OLAN, ARI, QUE, PALI, RIS) PP1M RIS/PALI	183 208 85	variable 78–234 variable	PP1M 302 days vs. COAPs 142 days; PP1M 428 days vs. AOAPs 229 days; PP1M 416 days vs. AOAPs 229 days
RLAI vs. AOAP *k* = 1, *n* = 85, age = 22.7, male = 84.4%												
Malla et al., 2016 [44]/ROLT/Canada	85 (77 analyzed)	Stabilization on RLAI/AOAP 18 RCT 86	Early-phase SS w/ PANSS total score of 60–120	*Time to stabilization and relapse*, *PANSS total*, *positive*, *and negative*, *CGI--S*	22.7	84.4	N/Av	100% < 3 years	RLAI AOAP (QUE, OLAN, RIS)	42 35	25–50 300–500, 15–20, 1–6	
No sig. differences in time to stabilization (likelihood ratio = 0.07; 95% CI = 0.651–1.75). No sig. improvements in PANSS total ($p = 0.95$), positive ($p = 0.66$), negative ($p = 0.83$), and CGI-S scores from BL to last visit												
PP1M vs. olanzapine *k* = 1, *n* = 57, age = 22.7, male = 64.9%												
Huang et al., 2018 [45]/DBT/China	57	13	SCZ w/ PANSS total score of 60–120	*PANSS total*, PANSS subscales, metabolic assessments	22.7	64.9	100	100% < 1 year	PP1M Oral OLAN	28 29	117, 156,2-34 5	No sig. difference between the 2 groups in any PANSS score
PP1M vs. paliperidone extended-release *k* = 1, *n* = 72, age = 46.4, male = 43.1%												
Bozzatello et al., 2019 [46]/ROLT/Italy	72	24	Clinically stable SCZ w/ a change in CGI-S score of ≤ 1	CGI-S	46.4	43.1	0	N/Av	PP1M PALI ER	36 36	50–150 6–12/day	Sig. effect between subjects was found for negative symptoms rated w/ the CGI-S ($p = 0.012$)
HD vs. PP1M *k* = 1, *n* = 290, age = 44.0, male = 74.5%												
Stroup et al., 2018 [47]/post hoc analysis of DBT [McEvoy et al., 2014 [48]]/USA	290	96	SZC or SAD at risk of relapse due to medication nonadherence or SA	*Efficacy failure*, tolerability failure	44.0	74.5	N/Av	N/Av	HD PP1M	145 145	25–200 39–234	An interaction between age and treatment ($p = 0.009$) revealed younger participants (18–45 years) assigned HD had longer time to efficacy failure than those assigned PP1M
PP1M vs. PP3M												

Table 1 (continued)

Reference/design/country	Total *N*	Duration (weeks)	Population	Outcome	Age (years)	% Male	% Hp at BL	Illness duration/age of onset	LAI/comparator	*N* per arm	Dose (mg)	Symptomatic efficacy
k = 1, *n* = 1429, age = 38.7, male = 53.0												
Savitz et al., 2016 [49]/DBT/Savitz et al., 2017 [50•], Mathews et al., 2018 [51], and Savitz et al., 2019 [52]/post hoc analyses/USA, EU, Japan, China, Russia	1429	Stabilization on PP1M 17 DBT 48	Clinically stable SCZ, PANSS total score < 70	*Relapse-free rates*, PANSS total score, PANSS subscale, Marder factor scores, CGI-S score Post hoc: *Symptomatic remission*; *Relapse-free survival*, PANSS total (analysis based on recent oral treatment); *Relapse-free survival* (analysis based on ethnicity)	38.7	53.0	61	N/Av	PP1M PP3M	504 (157 w/ recent oral RIS/P-ALI) 512 (166 w/ recent oral RIS/P-ALI	50, 75, 100, or 150 175, 263, 350, or 525	No sig. between-group difference in PANSS total score, PANSS subscale, Marder factor scores, CGI-S score. Similar symptomatic remission: PP3M 50.3%; PP1M 50.8% and combined remission (symptomatic and functional remission): PP3M 25.1%; PP1M 26.6%). Similar improvements in PANSS scores in recent-RIS/PALI (mean [SD] 18.3 [17.96]) and no-RIS/PALI (− 21.1 [16.40]) subgroups

AL = aripiprazole lauroxil, *AM* = active moiety, *ARI* = aripiprazole, *AOAP* = atypical oral antipsychotics, *AOM* = aripiprazole once-monthly, *AUC* = area under the curve, *BL* = baseline, *CGI-I* = Clinical Global Impression-Improvement, *CGI-S* = Clinical Global Impression-Severity, *CJS* = criminal justice system, *COAP* = conventional oral antipsychotic, *DBT* = double-blind trial, *DBPCT* = double-blind placebo-controlled trial, *HAL* = haloperidol, *HD* = haloperidol decanoate, *hp* = hospitalization, *LAI* = long-acting injectable, *MCF* = mean cumulative function, *N/Av* = not available, *OAP* = oral antipsychotic, *OLAN* = olanzapine, *PALI* = paliperidone, *PALI ER* = paliperidone extended-release, *PANSS* = Positive and Negative Syndrome Scale, *PBO* = placebo, *PER* = perphenazine, *PP1M* = paliperidone palmitate once-monthly, *PP3M* = paliperidone palmitate 3-monthly, *QUE* = quetiapine, *RCT* = randomized controlled trial, *RIS* = risperidone, *RLAI* = risperidone long-acting injectable, *ROLT* = randomized open-label trial, *SA* = substance abuse, *SAD* = schizoaffective disorder, *SCZ* = schizophrenia, *SD* = standard deviation, *SS* = schizophrenia spectrum disorder, *tx* = treatment, *w/* = with, *w/o* = without

Table 2 Randomized controlled trials of long-acting injectable antipsychotics: relapse and hospitalization

Reference/design/country	Total *N*	Duration (weeks)	Population	Outcome	Age (years)	% male	% Hp at BL	Illness duration/age of onset	LAI/comparator	*N* per arm	Dose (mg)	Relapse/hospitalization
PP3M vs. PBO *k* = 1, *n* = 119, age = 31.5, male = 72.3%												
Bell Lynum et al., 2018 [37]/post hoc analysis of DBPCT [Berwaerts et al., 2015 [38]]/Ukraine, USA, Romania, Colombia, Malaysia, Mexico, Turkey, South Korea	119	Stabilization on PP1M 17 DBPCT up to 2 years	Early illness SCZ (≤ 5 years) w/ PANSS total score < 120	*Time to relapse*, PANSS total, PANSS subscales, CGI-S	31.5	72.3	N/Av	100% ≤ 5 years	PP3M PBO	62 57	175, 263, 350, or 525	PP3M significantly delayed time to relapse vs. placebo (HR = 3.08 (95% CI = 1.08–8.80), *p* = 0.035) and reduced relapse rates (21.1 vs. 8.1%, *p* = 0.027)
PP1M vs. OAP *k* = 2, *n* = 444, age = 38.2, male = 86.2%												
Alphs et al., 2016 [39], Alphs et al., 2018 [40] and Starr et al., 2018 [41]/post hoc analyses of ROLT [Alphs et al., 2014 [42]]/USA	444	60	SCZ, taken into custody by the CJS ≥ 2 times in the previous 2 years w/ ≥ 1 leading to incarceration	*Mean number of tx failures (measured by MCF)*; *Time to first tx failure (analysis based on age of onset)*; *Time to first tx failure (analysis based on comorbid SA)*	38.2	86.3	N/Av	N/Av	PP1M OAPs: ARI, HAL, OLAN, PALI, PER, QEU, RIS	226 (130 w/ SA, 96 w/o SA, 42 ≤ 5 years, 183 > 5 years) 218 (134 w/ SA, 84 w/o SA, 35 ≤ 5 years, 182 > 5 years)	78–234 variable	Median (95% CI) time to first psych hp: W/ SA: PP1M 371 days, OAPs 317 days; w/o SA: PP1M > 450 days, OAPs 371 days
Kim et al., 2016 [43]/post hoc analysis of ROLT [Alphs et al., 2014 [42]]/USA	171 407 293	60	SCZ, taken into custody by the CJS ≥ 2 times in the previous 2 years w/ ≥ 1 leading to incarceration	*Time to first tx failure*	36.9 38.2 37.7	87.2 86.0 84.6	77% 79% 78%	22% ≤ 5 years 78% > 5 years 17% ≤ 5 years 83% > 5 years 18% ≤ 5 years 82% > 5 years	PP1M COAP (HAL, PER) PP1M AOAP (OLAN, ARI, QUE, PALI, RIS) PP1M RIS/PALI	136 35 224 183 208 85	78–234 variable 78–234 variable 78–234 variable 78–234 variable	Hospitalization: PP1M 8.1% COAPs 8.6% PP1M 8.0% AOAPs 12.6% PP1M 8.2% RIS/PALI 15.3%
RLAI vs. AOAP *k* = 1, *n* = 85, age = 22.7, male = 84.4%												
Malla et al., 2016 [44]/ROLT/Canada	85 (77 analyzed)	Stabilization on RLAI/AOAP 18 RCT 86	Early-phase SS w/ PANSS total score of 60–120	*Time to stabilization and relapse*, *PANSS total*, *positive*, *and negative*, *CGI-S*	22.7	84.4	N/Av	100% < 3 years	RLAI AOAP (QUE, OLAN, RIS)	42 35	25–50 300–500, 15–20, 1–6	Relapse: RLAI 26.2%, AOAP 14.3% (HR = 2.57, 95% CI = 0.15–1.25). No sig. differences in time to relapse (95% CI = 0.151–1.25) Hospitalization: RLAI 19.1%, AOAP 11.4%
HD vs. PP1M *k* = 1, *n* = 290, age = 44.0, male = 74.5%												
Stroup et al., 2018 [47]/post hoc analysis of DBT [McEvoy et al., 2014 [48]]/USA	290	96	SCZ or SAD at risk of relapse due to medication nonadherence or SA	*Efficacy failure*, tolerability failure	44.0	74.5	N/Av	N/Av	HD PP1M	145 145	25–200 39–234	Significantly more hospitalizations in younger participants with PP1M than with HD (31 vs. 14%, *p* = 0.02)
PP1M vs. PP3M *k* = 1, *n* = 1429, age = 38.7, male = 53.0												
Savitz et al., 2016 [49]/DBT/Savitz et al.,	1429	Stabilization on PP1M 17	Clinically stable SCZ, PANSS	*Relapse-free rates*, PANSS total score,	38.7	53.0	61	N/Av	PP1M PP3M	504 (157 w/ recent oral RIS/PALI)	50, 75, 100, or 150	Relapse: PP3M 7.7%; PP1M 9.2%;

Table 2 (continued)

Reference/design/country	Total *N*	Duration (weeks)	Population	Outcome	Age (years)	% male	% Hp at BL	Illness duration/age of onset	LAI/comparator	*N* per arm	Dose (mg)	Relapse/hospitalization
2017 [50], Mathews et al., 2018 [51], and Savitz et al., 2019 [52]/post hoc analyses/USA, EU, Japan, China, Russia		DBT 48	total score < 70	PANSS subscale, Marder factor scores, CGI-S score Post hoc: *Symptomatic remission*; *Relapse-free survival*, PANSS total (analysis based on recent oral treatment); *Relapse-free survival* (analysis based on ethnicity)						512 (166 w/ recent oral RIS/PALI	175, 263, 350, or 525	difference in relapse-free rate 1.2% [95% CI − 2.7%; 5.1%]). Similar relapse-free rates in recent-RIS/PALI (relapse-free rate [95% CI for difference] 2.6 [− 4.7 to 10.0]; PP3M 90%; PP1M 87%) and no-RIS/PALI subgroups (0.8 [− 4.5 to 6.0]; PP3M 92%; PP1M 91%). Similar relapse rates in Europeans (PP3M 7%; PP1M 8%) and non-Europeans (PP3M 9%; PP1M 10%)
PP3M vs. PBO *k* = 1, *n* = 119, age = 31.5, male = 72.3%												
Bell Lynum et al., 2018 [37]/post hoc analysis of DBPCT [Berwaerts et al., 2015 [38]]/Ukraine, USA, Romania, Colombia, Malaysia, Mexico, Turkey, and South Korea	119	Stabilization on PP1M 17 DBPCT variable 1–96	Early illness SCZ (≤ 5 years) w/ PANSS total score < 120	PSP	31.5	72.3	N/Av	100% ≤ 5 years	PP3M PBO	62 57	175, 263, 350, or 525	PP3M significantly delayed time to relapse vs. placebo (HR = 3.08 (95% CI = 1.08–8.80), p = 0.035) and reduced relapse rates (21.1 vs. 8.1%, p = 0.027)
PP1M vs. PP3M *k* = 1, *n* = 1016, age = 38.7, male = 53.0%												
Savitz et al., 2017 [50]/post hoc analysis of DBT [Savitz et al., 2016 [49]]/USA, EU, Japan, China, Russia	1016	48	Clinically stable SCZ w/ PANSS total score < 70, stabilized on PP1M	*PSP*	38.7	53.0	61	Mean age of onset 27.4 years	PP1M PP3M	504 512	50, 75, 100, or 150 175, 263, 350, or 525	Relapse: PP3M 7.7%; PP1M 9.2%
RLAI vs. AOAP *k* = 1, *n* = 85, age = 22.7, male = 84.4%												
Malla et al., 2016 [44]/ROLT/Canada	85 (77 analyzed)	Stabilization on RLAI/AOAP 18 86	Early-phase SS w/ PANSS total score of 60–120	*AIMS*, *SAS*, *BARS*, *DAI*	22.7	84.4	N/Av	100% < 3 years	RLAI AOAP (QUE, OLAN, RIS)	42 35	25–50 (400–500, 15–20, 1–6)	Relapse: RLAI 26.2%, AOAP 14.3% (HR = 2.57, 95% CI = 0.15–1.25). No sig. differences in time to relapse (95% CI = 0.151–1.25)

Table 2 (continued)

Reference/design/country	Total *N*	Duration (weeks)	Population	Outcome	Age (years)	% male	% Hp at BL	Illness duration/age of onset	LAI/comparator	*N* per arm	Dose (mg)	Relapse/hospitalization
												Hospitalization: RLAI 19.1%, AOAP 11.4%

AIMS = Abnormal Involuntary Movement Scale, *ARI* = aripiprazole, *AOAP* = atypical oral antipsychotics, *BARS* = Barnes Akathisia Rating Scale, *BL* = baseline, *CGI-S* = Clinical Global Impression-Severity, *CI* = confidence interval, *CJS* = criminal justice system, *COAP* = conventional oral antipsychotic, *DAI* = Drug Attitude Inventory, *DBT* = double-blind trial, *DBPCT* = double-blind placebo-controlled trial, *HAL* = haloperidol, *HD* = haloperidol decanoate, *hp* = hospitalization, *HR* = hazard ratio, *LAI* = long-acting injectable, *MCF* = mean cumulative function, *N/Av* = not available, *OAP* = oral antipsychotic, *OLAN* = olanzapine, *PALI* = paliperidone, *PANSS* = Positive and Negative Syndrome Scale, *PBO* = placebo, *PER* = perphenazine, *PP1M* = paliperidone palmitate once-monthly, *PP3M* = paliperidone palmitate 3-monthly, *psych* = psychiatric, *QUE* = quetiapine, *RCT* = randomized controlled trial, *RIS* = risperidone, *RLAI* = risperidone long-acting injectable, *ROLT* = randomized open-label trial, *SA* = substance abuse, *SAD* = schizoaffective disorder, *SAS* = Simpson-Angus Extrapyramidal Side Effects Scale, *SCZ* = schizophrenia, *SS* = schizophrenia spectrum disorder, *tx* = treatment, *w/* = with, *w/o* = without

In a second post hoc analysis of the same study [33], focusing on the subgroup of patients with severe psychotic symptoms (baseline PANSS total score above the median score of 92 ($n = 309$)), PANSS total ($p < 0.0001$) and subscale ($p < 0.0001$–$p < 0.0035$) scores improved significantly with both doses of AL vs. placebo [34]. Furthermore, both AL doses were associated with higher responder rates ≥ 30% PANSS total score decrease or CGI-I score of 2 or 1 (441 mg—49%, $p < 0.001$; 882 mg—61%, $p < 0.001$) vs. placebo (18%) [34] (Table 1).

Paliperidone Palmitate Once-Monthly Vs. Placebo In a post hoc analysis of a 2-year, DBPCT [36] (industry sponsor: Janssen) investigating a subgroup of 133 stabilized (paliperidone palmitate once-monthly (PP1M): flexible doses of 25, 50, 100 mg for 9 weeks), schizophrenia patients who all had relapsed after randomization to placebo ($n = 36$) or maintenance treatment with PP1M ($n = 97$), no significant differences were found in relapse symptom profiles, onset and severity of relapse symptoms, and post-relapse treatment response as measured by PANSS total ($p = 0.09$) and subscale scores ($p = 0.62$–$p = 0.95$) [35] (Table 1 and Table 2).

Paliperidone Palmitate 3-Monthly Vs. Placebo In a post hoc analysis of a DBPCT lasting up to 2 years (industry sponsor: Janssen) [38] investigating a subgroup of adults with early illness schizophrenia (duration ≤ 5 years) ($n = 119$) who were first stabilized on PP1M (78, 117, 156, or 234 mg) for 17 weeks and then randomized to paliperidone palmitate 3-monthly (PP3M) (175, 263, 350, or 525 mg) ($n = 62$) or placebo ($n = 57$), PP3M significantly delayed time to relapse vs. placebo (HR = 3.08 (95% CI = 1.08–8.80), $p = 0.035$) and reduced relapse rates (8.1 vs. 21.1%, $p = 0.027$) [37] (Table 2). Furthermore, PP3M was superior to placebo regarding PANSS total ($p = 0.003$), positive ($p = 0.011$), negative ($p = 0.019$), and general psychopathology ($p = 0.006$) subscale scores and CGI-S ($p = 0.025$) [37] (Table 1).

Head-to-Head Trials of LAIs Vs. Oral Antipsychotics

Paliperidone Palmitate Once-Monthly Vs. Oral Antipsychotics In four post hoc analyses of the same 15-month, randomized, open-label trial (ROLT) (industry sponsor: Janssen) of 444 individuals with schizophrenia and a history of incarceration, PP1M (flexible dosing 78–234 mg) ($n = 226$) was compared with clinicians' choice OAPs ($n = 218$) [42].

Results indicated that compared to clinicians' choice OAPs, PP3M was associated with a significantly lower mean cumulative function (MCF = mean number of events per person year of follow-up) of treatment failures (composite measure of psychiatric hospitalization; arrest or incarceration; suicide; treatment discontinuation due to inefficacy, safety, or tolerability; addition of

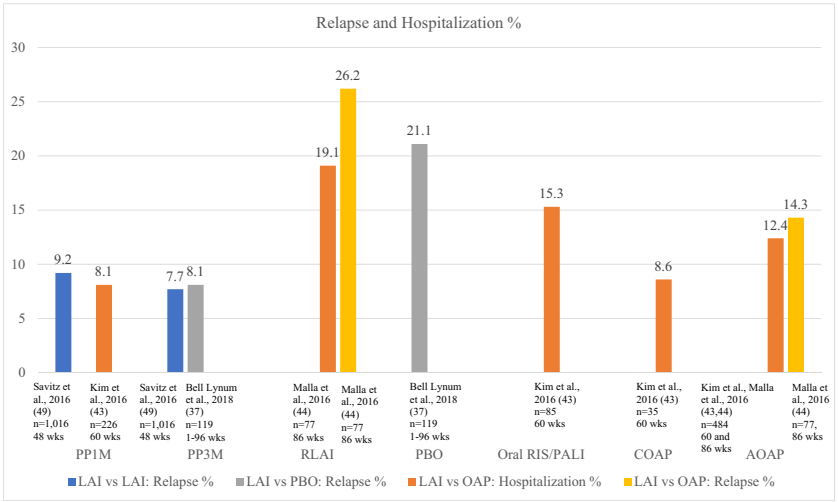

Fig. 1 Relapse and hospitalization rates

another antipsychotic due to inefficacy; or increased psychiatric services to prevent psychiatric hospitalization) (p = 0.007) as well as institutionalizations (arrests or incarcerations and/or psychiatric hospitalizations) (p = 0.005) [39] (Table 1 and Table 2). Furthermore, the relative advantage of PP1M over OAPs in reducing treatment failure was numerically greater in patients with recent-onset schizophrenia (HR = 1.73 (95% CI = 0.87–3.45), p = 0.121) vs. patients with more chronic schizophrenia (HR = 1.37 (95% CI = 1.02–1.85), p = 0.039) [40] (Table 1). Additionally, overall lower risk for treatment failure with PP1M was found both in patients with (HR = 1.48 (95% CI = 1.07–2.03), p = 0.016) and without comorbid substance abuse (HR = 1.77 (95% CI = 1.12–2.81), p = 0.015) [41] (Table 2). Median (95% CI) time to first treatment failure in the recent-onset population was >450 days in the PP1M group and 270 days in the OAP group; for subjects with more chronic illness [40], results were 416 days (PP1M) and 210 days (OAPs). In the substance abuse subgroup, time to first treatment failure was 291 days (PP1M) and 186 days (OAPs), being in the nonabuse cohort >450 (PP1M) and 284 days (OAPs) [41]. Moreover, subgroup analyses by OAP subgroups with reduced statistical power showed consistent results. Compared with PP1M, first treatment failure was 34% higher with conventional oral antipsychotics (COAPs) (HR = 1.34 (95% CI = 0.80–2.25), p = 0.262), 41% higher with atypical oral antipsychotics (AOAPs) (HR = 1.41 (95% CI = 1.06–1.88), p = 0.019), and 39% higher with oral paliperidone/risperidone (HR = 1.39 (95% CI = 0.97–1.99), p = 0.071) [43]. Similarly, hospitalization rates were numerically lower with PP1M (8.1%) than with oral COAPs (8.6%), oral AOAPs (12.6%), and oral paliperidone/risperidone (15.3%) [43] (Table 2), considering that OAP choice could be optimized based on past treatment response, while PP1M was the randomly assigned sole LAI choice.

Risperidone Long-Acting Injection Vs. Atypical Oral Antipsychotics In an exploratory, independently funded, 2-year, ROLT of 85 early-phase (≤3 years of illness) schizophrenia-spectrum disorder patients who were first stabilized for 18 weeks on risperidone long-acting injection (RLAI) (25–50 mg) or AOAPs and then randomized to RLAI (25–50 mg) (n = 42) or AOAPs (n = 35), time to stabilization (likelihood ratio = 0.07; 95% CI = 0.651–1.75) and time to relapse (likelihood ratio = 2.57; 95% CI = 0.151–1.25) were similar between RLAI and AOAPs [44]. However, only 16 patients in total relapsed (RLAI = 11 [26.2%], AOAP = 5 [14.3%]) and only 12 patients were admitted to hospitals (RLAI = 8 [19.1%], AOAP = 4 [11.4%]) [44] (Table 2), reducing the statistical power for the analysis of relapse and hospitalization rates.

Paliperidone Palmitate Once-Monthly Vs. Oral Olanzapine In a 13-week, double-blind trial (DBT) funded by the Chinese government in 57 first-episode schizophrenia patients who were randomly assigned to PP1M (117, 156, or 234 mg) or oral olanzapine (5 mg), PANNS total and subscale scores declined significantly (p < 0.001 each) in both groups in this highly responsive first-episode sample, without significant between-group differences [45] (Table 1).

Paliperidone Palmitate Once-Monthly Vs. Paliperidone Extended-Release In a 24-week, ROLT funded by the Italian government of 72 patients with stable but symptomatic schizophrenia who were randomized to PP1M (flexible dosing 50–150 mg) (n = 36) or oral paliperidone extended-release (6–12/day) (n = 36), PP1M was superior for negative symptoms rated with the Clinical Global Impression-Schizophrenia (CGI-SCH) scale (p = 0.012) [46] (Table 1).

Head-to-Head Trials of LAIs Vs. LAIs

Haloperidol Decanoate Vs. Paliperidone Palmitate Once-Monthly In a post hoc analysis of a 2-year, DBT funded by the National Institute of Mental Health in 290 patients with schizophrenia or schizoaffective disorder at risk of relapse, who were randomized to haloperidol decanoate (HD) (25–200 mg) (n = 145) or PP1M (39–234 mg) (n = 145) [48], younger participants (18–45 years) assigned to HD (n = 66) had a longer time to efficacy failure vs. PP1M (n = 75) (p = 0.009) [47]. Similarly, in younger patients, PP1M was associated with significantly more hospitalizations than HD (31 vs. 14%, p = 0.02) [47]. This finding differed from the results in the total group where no significant differences between HD and PP1M had been found regarding time to efficacy failure [47] (Table 2).

Paliperidone Palmitate Once-Monthly Vs. Paliperidone Palmitate 3-Monthly In a 48-week, DBT (industry sponsor: Janssen) in 1016 relatively stable schizophrenia patients who were first stabilized for 17 weeks on PP1M (50, 75, 100, or 150 mg) and then randomly assigned to PP3M (175, 263, 350, or 525 mg) (n = 512) or PP1M (50, 75, 100, or 150 mg) (n = 504), PP3M was noninferior to PP1M, as relapse rates were similar in both groups (PP3M = 8%; PP1M = 9%; difference in relapse-free rate 1.2%; 95% CI = −2.7 to 5.1%) [49]. PANSS total, PANSS subscale, PANSS Marder factor, and CGI-S scores confirmed the primary noninferiority result [49] (Table 2).

Three post hoc analyses of this DBT [49] revealed similarly respectable symptomatic remission rates (PP3M = 50.3%; PP1M = 50.8%) [50•]. Furthermore, relapse-free rates were similar in patients with (PP3M = 90%; PP1M = 87%) or without (PP3M = 92%; PP1M = 91%) recent prior use of oral risperidone/paliperidone [51], and in relapse rates for patients with an European (PP3M = 7%; PP1M = 8%) and non-European (PP3M = 9%; PP1M = 10%) background [52] (Table 2).

Efficacy of LAIs for Functional Outcomes and Quality of Life

In the 3-year period of this review, seven studies of LAIs (placebo-controlled: k = 4, OAP-controlled: k = 1; LAI–LAI comparisons: k = 3), which were post hoc analyses of previously published primary studies, investigated quality of life, subjective well-being, and functionality, including personal, social, and cognitive functioning, as well as readiness for work in patients with schizophrenia-spectrum disorders. Functional efficacy and quality of life results are summarized by individual LAI and specific study comparator in Table 3.

Placebo-Controlled Trials of LAIs

Aripiprazole Lauroxil Vs. Placebo In a post hoc analysis of a 12-week, DBPCT (industry sponsor: Alkermes) in 623 patients with acute schizophrenia that compared AL 441 mg (n = 207), AL 882 mg (n = 208), and placebo (n = 208) every 4 weeks [33], both AL groups significantly improved social functioning vs. placebo (p < 0.0001), measured by the 6- and 4-point PANSS Prosocial subscale and the Personal and Social Performance (PSP) total score, without any dose-related differences [54] (Table 3).

Paliperidone Palmitate Once-Monthly Vs. Placebo In a post hoc analysis of a 15-month, DBPCT (industry sponsor: Janssen), 334 patients with schizoaffective disorder (SAD) and acute worsening of psychotic and mood symptoms who were first stabilized for 25 weeks on PP1M (234 mg on day 1, 156 mg on day 8, flexible doses (78–234 mg) at/after day 36) and then randomly assigned to PP1M (78–234 mg) (n = 164) or placebo (n = 170) [56], improvements in all PSP domains (socially useful activities, personal/social relationships, self-sufficiency, and disruptive/aggressive behavior), observed during the randomized, open-label stabilization phase, were maintained during the double-blind phase with PP1M, but decreased in all four PSP domains during the double-blind phase with placebo (p < 0.008) [55] (Table 3).

Paliperidone Palmitate 3-Monthly Vs. Placebo In a post hoc analysis of a DBPCT (industry sponsor: Janssen) lasting up to 2 years [38] investigating a subgroup of adults with early illness schizophrenia (duration ≤ 5 years) (n = 119) who were first stabilized on PP1M (78, 117, 156, or 234 mg) for 17 weeks and then randomized to PP3M (175, 263, 350, or 525 mg) (n = 62) or placebo (n = 57), social functioning, measured by the PSP, was maintained with PP3M and significantly worsened with placebo (p = 0.016) [37] (Table 3).

Perseris Risperidone Vs. Placebo In a post hoc analysis of an 8-week, DBPCT (industry sponsor: Indivior) of 337 patients with acute schizophrenia, in which patients were randomized to RBP-7000 90 mg (n = 111), RBP-7000 120 mg (n = 114), or placebo (n = 112) [28•], RBP-7000 120 mg was significantly superior to placebo regarding health-related quality of life, measured with the EuroQol EQ-5D-5L Visual Analogue Scale (p = 0.0212) and the Subjective Well-Being Under Neuroleptic Treatment Scale-Short Version (SWN-S) total score (p = 0.0395) and in the domains physical functioning (p = 0.0093) and social integration (p = 0.0368) [53] (Table 3).

Head-to-Head Trials of LAIs Vs. Oral Antipsychotics

Paliperidone Palmitate Once-Monthly Vs. Paliperidone Extended-Release In a 24-week, ROLT funded by the Italian

Table 3 Randomized controlled trials of long-acting injectable antipsychotics: functional efficacy

Reference/design/country	Total *N*	Duration (weeks)	Population	Outcome	Age (years)	% male	% Hp at BL	Illness duration/age of onset	LAI/comparator	*N* per arm	Dose (mg)	Functional efficacy
AL vs. PBO *k* = 1, *n* = 623, age = 39.7, male = 67.9%												
Correll et al., 2019 [54]/post hoc analysis of DBPCT [Meltzer et al., 2015 [33]]/USA	623 (596 analyzed)	12	Acutely exacerbated SCZ w/ PANSS total score of 70–120	*PANSS Prosocial subscales* *PSP*	39.7	67.9	100	N/Av	AL PBO	207 208 208	441 882	PANSS Prosocial subscale and PSP total score improved significantly w/ AL vs. PBO ($p < 0.0001$)
PP1M vs. PBO *k* = 1, *n* = 334, age = 38.6, male = 50.6%												
Fu et al., 2018 [55]/post hoc analysis of DBPCT [Fu et al., 2015 [56]]/USA	334	Stabilization on PP1M 25 DBPCT 60	Acutely exacerbated SAD	*PSP*	38.6	50.6	31	36% ≤ 5 years, 64% > 5 years	PP1M PBO	164 170	78–234	Differences w/ PP1M compared to PBO were sig. in all 4 PSP domains ($p \leq 0.008$)
PP3M vs. PBO *k* = 1, *n* = 119, age = 31.5, male = 72.3%												
Bell Lynum et al., 2018 [37]/post hoc analysis of DBPCT [Berwaerts et al., 2015 [38]]/Ukraine, USA, Romania, Colombia, Malaysia, Mexico, Turkey, and South Korea	119	Stabilization on PP1M 17 DBPCT variable 1–96	Early illness SCZ (≤ 5 years) w/ PANSS total score < 120	PSP	31.5	72.3	N/Av	100% ≤ 5 years	PP3M PBO	62 57	175, 263, 350, or 525	PSP total scores were maintained w/ PP3M and worsened in the PBO group: mean (SD) changes PP3M (− 0.4 [7.2]; $p = 0.660$); PBO (− 3.5 [10.3]; $p = 0.016$). LS mean (95% CI) difference in change between the 2 treatment groups was − 3.8 (− 7.2, − 0.4; $p = 0.031$)
RBP-7000 vs. PBO *k* = 1, *n* = 337, age = 41.2, male = 76.5%												
Isitt et al., 2016 [53]/post hoc analysis of DBPCT [Nasser et al., 2016 [28•]]/USA	337	8	Acutely exacerbated SCZ w/ PANSS total of 80–120	*EuroQol EQ-5D-5L*, *SWN-S*	41.2	76.5	100	N/Av	RBP-7000 PBO	111 114 112	90 120	EQ-5D-5L VAS increased significantly in RBP-7000 120 mg compared to PBO ($p = 0.0212$). Sig. improvements in SWN-S total score and SWN-S domains physical functioning ($p = 0.0093$) and social integration ($p = 0.0395$)
PP1M vs. paliperidone extended-release *k* = 1, *n* = 72, age = 46.4, male = 43.1%												
Bozzatello et al., 2019 [46]/ROLT/Italy	72	24	Clinically stable SCZ w/ a change in CGI-S score of ≤ 1	PSP, SWN-S	46.4	43.1	0	N/Av	PP1M PALI ER	36 36	50–150 6–12/day	No sig. results for PSP/SWN-S
AOM vs. PP1M *k* = 1, *n* = 295, age = 41.9, male = 59.8%												
Potkin et al., 2017 [57], 2017 [58]/post hoc analyses of ROLT [Naber et al., 2015 [59]]/USA	295	28	Clinically stable SCZ w/ CGI-S score of 3–5	*WoRQ*, *QLS*, *CGI-S*, *CGI-I*, *SWN-S*, *TooL*	41.9	59.8	N/Av	Mean illness duration 14.25 years	AOM PP1M	148 147	400 75–150	WoRQ total score was significantly better for AOM ($p = 0.004$). Significantly more CGI-S and CGI-I responders w/ AOM (aOR, 2.26; $p = 0.010$, and 2.51; $p = 0.0032$) and significantly better CGI-I scores (LS mean tx difference, −0.326; 95%

Table 3 (continued)

Reference/design/country	Total *N*	Duration (weeks)	Population	Outcome	Age (years)	% male	% Hp at BL	Illness duration/age of onset	LAI/comparator	*N* per arm	Dose (mg)	Functional efficacy
												CI, −0.60 to −0.05; p = 0.020). Larger improvements w/ AOM for SWN-S and TooL. Shifts toward work readiness were significantly associated with greater QLS improvements at week 28 (p < 0.0001)
RLAI vs. PP1M k = 1, n = 30, age = 45.0, male = 52.4%												
Koshikawa et al., 2016 [60]/ROLT/Takekita et al., 2016 [61]/post hoc analysis/Japan	30 (21 analyzed)	24	Nonacute SCZ or SAD w/ PANSS total score ≤ 120	*SFS*, *BACS*	45.0	52.4	0	Mean age of onset 31.1	RLAI PP1M	16 14	Flexibly up to 50 mg/2 weeks Flexibly up to 150 mg/4 weeks	SFS improved significantly more w/ PP1M vs. RLAI (total, p = 0.038; competence, p = 0.001, and performance, p = 0.007). BACS score for the attention and processing speed item showed higher improvement in the PP1M group than the RLAI group (p = 0.039). No differences in PANSS, DIEPSS, or SWN-S total score changes
PP1M vs. PP3M k = 1, n = 1016, age = 38.7, male = 53.0%												
Savitz et al., 2017 [50•]/post hoc analysis of DBT [Savitz et al., 2016 [49]]/USA, EU, Japan, China, Russia	1016	48	Clinically stable SCZ w/ PANSS total score < 70, stabilized on PP1M	*PSP*	38.7	53.0	61	Mean age of onset 27.4 years	PP1M PP3M	504 512	50, 75, 100, or 150 175, 263, 350, or 525	Patients of both groups achieved functional remission (defined as PSP score > 70, PP3M 42.5%; PP1M 43.9%) and combined remission (symptomatic and functional remission, PP3M 25.1%; PP1M 26.6%)

AOM = aripiprazole once-monthly, *aOR* = adjusted odds ratio, *BACS* = Brief Assessment of Cognition in Schizophrenia, *BL* = baseline, *CGI-S* = Clinical Global Impression-Severity, *CGI-I* = Clinical Global Impression-Improvement, *CI* = confidence interval, *DAI* = Drug Attitude Inventory, *DBT* = double-blind trial, *DBPCT* = double-blind placebo-controlled trial, *hp* = hospitalization, *LAI* = long-acting injectable, *LS* = least squares, N/Av = not available, *PALI ER* = paliperidone extended-release, *PANSS* = Positive and Negative Syndrome Scale, *PBO* = placebo, *PP1M* = paliperidone palmitate once-monthly, *PP3M* = paliperidone palmitate 3-monthly, *PSP* = Personal and Social Performance, *QLS* = Heinrichs Carpenter Quality of Life Scale, *RLAI* = risperidone long-acting injectable, *ROLT* = randomized open-label trial, *SAD* = schizoaffective disorder, *SWN-S* = Subjective Well-Being Under Neuroleptics Scale-Short Form, *SCZ* = schizophrenia, *SD* = standard deviation, *SFS* = Social Functioning Scale, *tx* = treatment, *TooL* = Tolerability and Quality of Life Questionnaire, *VAS* = visual analogue scale, *WoRQ* = Work Readiness Questionnaire, *w/* = with

government of 72 patients with stable but symptomatic schizophrenia who were randomized to PP1M (flexible dosing 50–150 mg) ($n = 36$) or paliperidone extended-release (6–12/day) ($n = 36$), no significant between-group emerged regarding PSP ($p = 0.103$) and SWN-S ($p = 0.65$) scores [46] (Table 3).

Head-to-Head Trials of LAIs Vs. LAIs

Aripiprazole Once-Monthly 400 mg Vs. Paliperidone Palmitate Once-Monthly In two post hoc analyses of a 28-week, ROLT (industry sponsor: Otsuka and Lundbeck) of 295 relatively stable schizophrenia patients with reasons for a treatment change, AOM 400 mg ($n = 148$) was compared with PP1M (flexible dosing 75–150 mg) ($n = 147$), each injected intramuscularly every 4 weeks [59], several additionally analyzed outcomes favored AOM.

For example, compared with PP1M, AOM improved the Work Readiness Questionnaire (WoRQ) total score significantly more ($p = 0.004$), and more patients were ready for work at study endpoint (52.7 vs. 32.7%, $p = 0.003$) [58]. Furthermore, compared to PP1M, AOM was associated with significantly lower (better) CGI-I scores ($p = 0.02$) and significantly more responders based on CGI-S (62.7 vs. 43.5%, $p = 0.010$) and CGI-I (52.0 vs. 29.4%, $p = 0.0032$) assessed openly [58]. Different from the primary outcome, the Heinrich-Carpenter QLS scale that was assessed by masked raters and had shown significant superiority of AOM [58], only numerically larger improvements with AOM on the openly assessed Tolerability and Quality of Life (TooL) questionnaire and the SWN-S treatment satisfaction were observed [62] (Table 1). In an additional analysis, shifts toward work readiness were significantly associated with greater Heinrich-Carpenter QLS improvements at week 28 ($p < 0.0001$), and QLS total scores significantly predicted work readiness at week 28 [57] (Table 3). Although, overall, these results favored AOM over PP1M, results must be interpreted with caution, as they were based on unblinded assessments and as results favored the study sponsor.

Risperidone Long-Acting Injection Vs. Paliperidone Palmitate Once-Monthly In a 6-month, independently funded pilot ROLT of 30 patients with nonacute schizophrenia or SAD, comparing RLAI ($n = 16$) dosed flexibly up to 50 mg/2 weeks with PP ($n = 14$) dosed flexibly up to 150 mg/4 weeks, PP1M was superior to RLAI on the Social Functioning Scale (SFS) total ($p = 0.038$) and subscale scores (competence: $p = 0.001$, performance: $p = 0.007$) [60] (Table 1). In a post hoc analysis of the same ROLT [60], RLAI was superior to PP1M on the combined Brief Assessment of Cognition in Schizophrenia (BACS) item attention and speed processing ($p = 0.039$) [61] (Table 3).

Paliperidone Palmitate Once-Monthly Vs. Paliperidone Palmitate 3-Monthly In a 48-week, DBT (industry sponsor: Janssen) in 1016 relatively stable schizophrenia patients who were first stabilized for 17 weeks on PP1M (50, 75, 100, or 150 mg) and then randomly assigned to PP3M (175, 263, 350, or 525 mg) ($n = 512$) or PP1M (50, 75, 100, or 150 mg) ($n = 504$) [49], both groups were comparable regarding functional remission, defined as a PSP score > 70, in the last 6 months of the double-blind phase (PP3M 42.5%, PP1M 43.9%) [50•] (Table 3).

Tolerability and Safety of LAIs

To assess metabolic as well as extrapyramidal symptom (EPS)-related adverse effects (AEs), five studies of LAIs (placebo-controlled: $k = 1$, OAP-controlled: $k = 1$, LAI–LAI comparisons: $k = 3$), of which 4 were post hoc analyses, were conducted in patients with schizophrenia-spectrum disorders. Adverse results are summarized by individual LAI and specific study comparator in Table 4.

Placebo-Controlled Trials of LAIs

Aripiprazole Lauroxil Vs. Placebo In a post hoc analysis of a 12-week, DBPCT (industry sponsor: Alkermes) in 623 patients with acute schizophrenia that compared AL 441 mg ($n = 207$), AL 882 mg ($n = 208$), and placebo ($n = 208$) every 4 weeks [33], changes in serum lipid, lipoprotein, plasma glucose, or HbA1c value were not clinically relevant in all groups [63]. Prolactin levels decreased for both doses of the partial D2 agonist AL and not with placebo [63] (no p values provided). The mean (SD) change for body weight was 0.74 (3.9) kg, 0.86 (3.7) kg, and 0.01 (3.6) kg for AL 441 mg, AL 882 mg, and placebo groups, respectively (no p values provided) [63]. Overall, metabolic AEs were reported in 2.4, 1.4, and 2.4% of patients in the AL 441 mg, AL 882 mg, and placebo groups, respectively [63] (Table 4).

Head-to-Head Trials of LAIs vs. Oral antipsychotics

Risperidone Long-Acting Injections Vs. Atypical Oral Antipsychotics In an exploratory, 2-year, independently funded ROLT, 85 individuals in early phase (≤ 3 years of illness) of a schizophrenia-spectrum disorder who were first stabilized for 18 weeks on RLAI (25–50 mg) or AOAPs, respectively, and then randomly assigned to RLAI (25–50 mg) ($n = 42$) or AOAPs ($n = 35$), no statistically significant between-group difference for any tolerability measure was found, although numerically less patients experience akathisia with RLAI during (RLAI 5.6%; AOAPs 10.3%) and following (RLAI 7.7%; AOAPs 9.2%) stabilization [44] (Table 4).

Table 4 Randomized controlled trials of long-acting injectable antipsychotics: tolerability/safety

Reference/design/country	Total *N*	Duration (weeks)	Population	Outcome	Age (years)	% male	% Hp at BL	Illness duration/age of onset	LAI/comparator	*N* per arm	Dose (mg)	Tolerability/safety
RBP-7000 vs. PBO *k* = 1, *n* = 337, age = 41.2, male = 77.5%												
Nasser et al., 2016 [28•]/DBPCT/Ivaturi et al., 2017 [29]/post hoc analysis/USA	337	8	Acutely exacerbated SCZ w/ PANSS total of 80–120	*PANSS total*, CGI-S Post hoc: *Total AM plasma exposure*, PANSS total, CGI-S	41.2	76.5	N/Av	N/Av	RBP-7000 PBO	111 114 112	90 120	Most frequently: weight gain, and akathisia. Overall incidence of EPS-related AEs was low and similar across groups
AL_{NCD} vs. AL *k* = 1, *n* = 160, age = 44.0, male = 73.3%												
Hard et al., 2018 [27]/DBPCT/USA	161	24	Clinically stable SCZ or SAD	*Mean plasma concentrations*	44.0	73.3	0	N/Av	AL, oral ARI, AL_{NCD}, + 20 days oral PBO AL, oral ARI, PBO, + 20 days oral ARI	39 and 41 40 and 41	441 or 882 + 30 441 or 882 + 15	AL 441-mg/1-day initiation and AL 882-mg/1-day initiation groups—66.7 and 68.3% AL 441-mg and AL 882--mg/21-day initiation groups—60.0 and 68.3%
AL vs. PBO *k* = 1, *n* = 623, age = 39.7, male = 67.9%												
Potkin et al., 2017 [34]/post hoc, subgroup analysis of DBPCT [Meltzer et al., 2015 [33]]/USA, Ukraine, Russia, Bulgaria, Romania, Philippines, Malaysia	309 (294 analyzed)	12	Acutely exacerbated SCZ w/ PANSS total above the median score of 92	*PANSS total*, PANSS subscales	39.7	69.0	100	N/Av	AL PBO	100 104 105	441 882	Most common (≥ 5% in any tx group): SCZ, akathisia, headache, insomnia, anxiety
PP1M vs. PBO *k* = 1, *n* = 133, age = 39.4, male = 54.1%												
Emsley et al., 2018 [35]/post hoc and subgroup analysis of DBPCT [Hough et al., 2010 [36]]/South Africa	133	Stabilization on PP1M 9, DBPCT 96	Relapsed SCZ patients	*PANSS total*, PANSS domains	39.4	54.1	N/Av	100% ≥ 1 year	PP1M PBO	97 36	25, 50 or 100	No elevated blood pressure or heart rate, dyskinesia, antipsychotic tolerance, or elevated prolactin
PP3M vs. PBO *k* = 1, *n* = 119, age = 31.5, male = 72.3%												
Bell Lynum et al., 2018 [37]/post hoc analysis of DBPCT [Berwaerts et al., 2015 [38]]/Ukraine, USA, Romania, Colombia, Malaysia, Mexico, Turkey, South Korea	119	Stabilization on PP1M 17 DBPCT up to 2 years	Early illness SCZ (≤ 5 years) w/ PANSS total score < 120	*Time to relapse*, PANSS total, PANSS subscales, CGI-S	31.5	72.3	N/Av	100% ≤ 5 years	PP3M PBO	62 57	175, 263, 350, or 525	Most common (≥ 2): weight increase (12.9 vs. 3.5%), anxiety (9.7 vs. 8.8%), nasopharyngitis (8.1 vs. 3.5%), headache (8.1 vs. 1.8%), urinary tract infection (6.5 vs. 0.0%), and akathisia (3.2 vs. 0.0%), respectively
PP1M vs. OAP *k* = 2, *n* = 444, age = 38.2, male = 86.2%												
Alphs et al., 2016 [39], Alphs et al., 2018 [40] and Starr et al., 2018 [41]/post hoc analyses of ROLT [Alphs et al., 2014	444	60	SCZ, taken into custody by the CJS ≥ 2 times in the	*Mean number of tx failures (measured by MCF)*;	38.2	86.3	N/Av	N/Av	PP1M OAPs: ARI, HAL, OLAN, PALI, PER, QEU, RIS	226 (130 w/ SA, 96 w/o SA, 42 ≤ 5	78–234 variable	PP1M 86.3% OAPs 81.7% Recent onset: PP1M 90.5%, OAPs 77.1%

Table 4 (continued)

Reference/design/country	Total *N*	Duration (weeks)	Population	Outcome	Age (years)	% male	% Hp at BL	Illness duration/age of onset	LAI/comparator	*N* per arm	Dose (mg)	Tolerability/safety
[42]]/USA			previous 2 years w/ ≥ 1 leading to incarceration	*Time to first tx failure (analysis based on age of onset)*; *Time to first tx failure (analysis based on comorbid SA)*						years, 183 > 5 years) 218 (134 w/ SA, 84 w/o SA, 35 ≤ 5 years, 182 > 5 years)		Chronic illness: PP1M 84.7%, OAPs 80.2% W/ SA: PP1M 87.7%, OAPs 83.6% W/o SA: PP1M 84.4%, OAPs 78.6%
Kim et al., 2016 [43]/post hoc analysis of ROLT [Alphs et al., 2014 [42]]/USA	171 407 293	60	SCZ, taken into custody by the CJS ≥ 2 times in the previous 2 years w/ ≥ 1 leading to incarceration	*Time to first tx failure*	36.9 38.2 37.7	87.2 86.0 84.6	77% 79% 78%	22% ≤ 5 years 78% > 5 years 17% ≤ 5 years 83% > 5 years 18% ≤ 5 years 82% > 5 years	PP1M COAP (HAL, PER) PP1M AOAP (OLAN, ARI, QUE, PALI, RIS) PP1M RIS/PALI	136 35 224 183 208 85	78–234 variable 78–234 variable 78–234 variable	COAP 91.4%, AOAP 77.6% PALI/RIS 77.6%
PP1M vs. olanzapine *k* = 1, *n* = 57, age = 22.7, male = 64.9%												
Huang et al., 2018 [45]/DBT/China	57	13	SCZ w/ PANSS total score of 60–120	*PANSS total*, PANSS subscales, metabolic assessments	22.7	64.9	100	100% < 1 year	PP1M Oral OLAN	28 29	117, 156,23-4 5	No sig. difference between the groups in BMI ($F = 0.00$, $p = 0.947$)
PP1M vs. paliperidone extended-release *k* = 1, *n* = 72, age = 46.4, male = 43.1%												
Bozzatello et al., 2019 [46]/ROLT/Italy	72	24	Clinically stable SCZ w/ a change in CGI-S score of ≤ 1	CGI-S	46.4	43.1	0	N/Av	PP1M PALI ER	36 36	50–150 6–12/day	Mild to moderate including agitation (10.7%), EPS (10.7%), gastrointestinal symptoms (9.2%), sedation (9.2%), and insomnia (7.7%)
HD vs. PP1M *k* = 1, *n* = 290, age = 44.0, male = 74.5%												
Stroup et al., 2018 [47]/post hoc analysis of DBT [McEvoy et al., 2014 [48]]/USA	290	96	SZC or SAD at risk of relapse due to medication nonadherence or SA	*Efficacy failure*, tolerability failure	44.0	74.5	N/Av	N/Av	HD PP1M	145 145	25–200 39–234	An interaction of treatment and age on akathisia ($p = 0.047$) found an advantage for PP1M that was larger among younger persons. Advantage for HD on serum prolactin levels was larger among younger women ($p = 0.033$)
PP1M vs. PP3M *k* = 1, *n* = 1429, age = 38.7, male = 53.0												
Savitz et al., 2016 [49]/DBT/Savitz et al., 2017 [50], Mathews et al., 2018 [51], and Savitz	1429	Stabilization on PP1M 17 DBT 48	Clinically stable SCZ, PANSS	*Relapse-free rates*, PANSS total score,	38.7	53.0	61	N/Av	PP1M PP3M	504 (157 w/ recent oral	50, 75, 100, or 150	PP3M 68%, PP1M 66% Most common (21% each): weight gain (also in both

Table 4 (continued)

Reference/design/country	Total *N*	Duration (weeks)	Population	Outcome	Age (years)	% male	% Hp at BL	Illness duration/age of onset	LAI/comparator	*N* per arm	Dose (mg)	Tolerability/safety
et al., 2019 [52]/post hoc analyses/USA, EU, Japan, China, Russia			total score < 70	PANSS subscale, Marder factor scores, CGI-S score Post hoc: *Symptomatic remission*; *Relapse-free survival*, PANSS total (analysis based on recent oral treatment); *Relapse-free survival* (analysis based on ethnicity)						RIS/P-ALI) 512 (166 w/ recent oral RIS/P-ALI	175, 263, 350, or 525	subgroup analyses). Less TEAEs in Europeans (PP3M 56%, PP1M 59%) than non-Europeans (PP3M 80%, PP1M 73%)
PP3M vs. PBO *k* = 1, *n* = 119, age = 31.5, male = 72.3%												
Bell Lynum et al., 2018 [37]/post hoc analysis of DBPCT [Berwaerts et al., 2015 [38]]/Ukraine, USA, Romania, Colombia, Malaysia, Mexico, Turkey, and South Korea	119	Stabilization on PP1M 17 DBPCT variable 1–96	Early illness SCZ (≤ 5 years) w/ PANSS total score < 120	PSP	31.5	72.3	N/Av	100% ≤ 5 years	PP3M PBO	62 57	175, 263, 350, or 525	Most common (≥ 2%) (PP1M vs. PBO): weight increase (12.9 vs. 3.5%), anxiety (9.7 vs. 8.8%), nasopharyngitis (8.1 vs. 3.5%), headache (8.1 vs. 1.8%), urinary tract infection (6.5 vs. 0.0%), and akathisia (3.2 vs. 0.0%), respectively
PP1M vs. paliperidone extended-release *k* = 1, *n* = 72, age = 46.4, male = 43.1%												
Bozzatello et al., 2019 [46]/ROLT/Italy	72	24	Clinically stable SCZ w/ a change in CGI-S score of ≤ 1	PSP, SWN-S	46.4	43.1	0	N/Av	PP1M PALI ER	36 36	50–150 6–12/day	Mild to moderate including agitation (10.7%), EPS (10.7%), gastrointestinal symptoms (9.2%), sedation (9.2%), and insomnia (7.7%)
AL vs. PBO *k* = 1, *n* = 623, age = 39.7, male = 67.9%												
Nasrallah et al., 2016 [63]/post hoc analysis of DBPCT [Meltzer et al., 2015 [33]]/USA	623	12	Acutely exacerbated SCZ w/ PANSS total score of 70–120	*Body weight*, *BMI*, *fasting blood glucose and serum lipids*, *glycosylated hemoglobin (HbA1c)*,	39.7	67.9	100	N/Av	AL PBO	207 208 208	441 882	No clinically relevant changes in any serum lipid, lipoprotein, plasma glucose, or HbA1c value. Prolactin levels decreased in all groups. Mean (SD) change for body weight was 0.74 (3.9) kg, 0.86 (3.7) kg, and 0.01 (3.6) kg for AL 441-mg, AL 882-mg, and

Table 4 (continued)

Reference/design/country	Total *N*	Duration (weeks)	Population	Outcome	Age (years)	% male	% Hp at BL	Illness duration/age of onset	LAI/comparator	*N* per arm	Dose (mg)	Tolerability/safety
				and prolactin								PBO groups, respectively. AEs related to metabolic parameters: AL 441 mg 2.4%, 882 mg 1.4%, PBO 2.4%
RLAI vs. AOAP *k* = 1, *n* = 85, age = 22.7, male = 84.4%												
Malla et al., 2016 [44]/ROLT/Canada	85 (77 analyzed)	Stabilization on					RLAI/AOAP 18 86	Early-phase SS w/ PANSS total score of 60–120	*AIMS*, *SAS*, *BARS*, *DAI*	22.7	84.4	N/Av
100% < 3 years	RLAI AOAP (QUE, OLAN, RIS)	42 35	25–50 (400–500, 15–20, 1–6)	No sig. change in AIMS or SAS scores in either group. BARS: small number of patients experienced akathisia during [(RLAI 5.6%); oral 10.3%] and following [(RLAI 7.7%); oral 9.2%] stabilization with no sig.				between-group differences				
PP1M vs. PP3M *k* = 1, *n* = 1429, age = 38.7, male = 53.0%												
Sliwa et al., 2018 [64] and Mathews et al., 2018 [65]/post hoc analyses of DBPCT [Savitz et al., 2016 [49]]/USA, EU, Japan, China, Russia	1016	Stabilization on PP1M 17 DBT 48	Clinically stable SCZ w/ PANSS total score < 70	*Injection site reactions and pain (4-point scale and VAS)* *Overall incidence, TTO, and TTR of EPS-related TEAEs*	38.7	53.0	61	N/Av	PP1M PP3M	504 512	50–150 175–525	Incidence of induration, redness, and swelling 7–13%. VAS scores decreased from OL-BL to DB-BL and DB-endpoint. Overall incidence of EPS-related TEAEs decreased from 12.6% in the OL phase (PP1M) to 7.4% (PP1M) in the DB phase; median TTO for all EPS-related TEAEs was 17 days (PP1M) in OL phase and 115 days (PP3M) and 98.5 days (PP1M) in DB phase; median TTR was 36.5 days (PP1M) in OL phase and 91 days (PP3M) and 85.5 days (PP1M) in DB phase

Table 4 (continued)

Reference/design/country	Total *N*	Duration (weeks)	Population	Outcome	Age (years)	% male	% Hp at BL	Illness duration/age of onset	LAI/comparator	*N* per arm	Dose (mg)	Tolerability/safety
AOM vs. PP1M *k* = 1, *n* = 295, age = 41.9, male = 59.8%												
Potkin et al., 2017 [66]/post hoc analyses of ROL [Naber et al., 2015 [59]]/USA	295	28	Clinically stable SCZ w/ CGI-S score of 3–5	*Serum prolactin concentrations* *ASEX*	41.9	59.8	N/Av	Mean illness duration 14.25 years	AOM PP1M	148 147	400 75–150	Odds for sexual dysfunction were lower w/ AOM vs. PP1M (aOR [95% CI], 0.29 [0.14–0.61]; $p = 0.0012$) in men (0.33 [0.13–0.86]; $p = 0.023$), women (0.14 [0.03–0.62]; $p = 0.0099$), and patients aged 18–35 years (0.04 [< 0.01–0.34]; $p = 0.003$). Mean (SD) prolactin concentrations decreased w/ AOM and increased w/ PP1M
PP1M vs. PP3M *k* = 1, *n* = 1429, age = 38.7, male = 53.0%												
Sliwa et al., 2018 [64] and Mathews et al., 2018 [65]/post hoc analyses of DBPCT [Savitz et al., 2016 [49]]/USA, EU, Japan, China, Russia	1016	Stabilization on PP1M 17 DBT 48	Clinically stable SCZ w/ PANSS total score < 70	*Injection site reactions and pain (4-point scale and VAS)* *Overall incidence, TTO, and TTR of EPS-related TEAEs*	38.7	53.0	61	N/Av	PP1M PP3M	504 512	50–150 175–525	Incidence of induration, redness, and swelling 7–13%. VAS scores decreased from OL-BL to DB-BL and DB-endpoint. Overall incidence of EPS-related TEAEs decreased from 12.6% in the OL phase (PP1M) to 7.4% (PP1M) in the DB phase; median TTO for all EPS-related TEAEs was 17 days (PP1M) in OL phase and 115 days (PP3M) and 98.5 days (PP1M) in DB phase; median TTR was 36.5 days (PP1M) in OL phase and 91 days (PP3M) and 85.5 days (PP1M) in DB phase
AOM vs. PP1M *k* = 1, *n* = 295, age = 41.9, male = 59.8%												
Potkin et al., 2017 [66]/post hoc analyses of ROL [Naber et al., 2015 [59]]/USA	295	28	Clinically stable SCZ w/ CGI-S score of 3–5	*Serum prolactin concentrations* *ASEX*	41.9	59.8	N/Av	Mean illness duration 14.25 years	AOM PP1M	148 147	400 75–150	Odds for sexual dysfunction were lower w/ AOM vs. PP1M (aOR [95% CI], 0.29 [0.14–0.61]; $p = 0.0012$) in men (0.33 [0.13–0.86]; $p = 0.023$), women (0.14 [0.03–0.62]; $p = 0.0099$), and patients aged 18–35 years (0.04 [< 0.01–0.34]; $p = 0.003$). Mean (SD) prolactin concentrations decreased w/ AOM and increased w/ PP1M
PP1M vs. paliperidone extended-release *k* = 1, *n* = 72, age = 46.4, male = 43.1%												
Bozzatello et al., 2019 [46]/ROLT/Italy	72	24	Clinically stable SCZ w/ a change	*TSQM, SES*	46.4	43.1	0	N/Av	PP1M PALI ER	36 36	50–150 6–12/day	Mild to moderate including agitation (10.7%), extrapyramidal symptoms

Table 4 (continued)

Reference/design/country	Total *N*	Duration (weeks)	Population	Outcome	Age (years)	% male	% Hp at BL	Illness duration/age of onset	LAI/comparator	*N* per arm	Dose (mg)	Tolerability/safety
			in CGI-S score of ≤ 1									(10.7%), gastrointestinal symptoms (9.2%), sedation (9.2%), and insomnia (7.7%)

AE = adverse events, *AIMS* = Abnormal Involuntary Movement Scale, *AL* = aripiprazole lauroxil, *ALNCD* = aripiprazole lauroxil nanocrystal dispersion, *AM* = active moiety, *AOM* = aripiprazole once-monthly, *aOR* = adjusted odds ratio, *ASEX* = Arizona Sexual Experience Scale, *BARS* = Barnes Akathisia Rating Scale, *BL* = baseline, *BMI* = body mass index, *CGI-S* = Clinical Global Impression-Severity, *CI* = confidence interval, *DAI* = Drug Attitude Inventory, *DB* = double-blind, *DBT* = double-blind trial, *DBPCT* = double-blind placebo-controlled trial, *EPS* = extrapyramidal syndrome, *HAL* = haloperidol, *HD* = haloperidol decanoate, *hp* = hospitalization, *LAI* = long-acting injectable, *N/Av* = not available, *MCF* = mean cumulative function, *OL* = open-label, *OLAN* = olanzapine, *PALI* = paliperidone, *PALI ER* = paliperidone extended-release, *PANSS* = Positive and Negative Syndrome Scale, *PBO* = placebo, *PP1M* = paliperidone palmitate once-monthly, *PP3M* = paliperidone palmitate 3-monthly, *PSP* = Personal and Social Performance, *SWN-S* = Subjective Well-Being Under Neuroleptics Scale-Short Form, *QUE* = quetiapine, *RIS* = risperidone, *RLAI* = risperidone long-acting injectable, *ROLT* = randomized open-label trial, *SA* = substance abuse, *SAD* = schizoaffective disorder, *SAS* = Simpson-Angus Extrapyramidal Side Effects Scale, *SCZ* = schizophrenia, *SES* = Service Engagement Scale, *TEAE* = treatment-emergent adverse events, *TSQM* = Treatment Satisfaction Questionnaire for Medication, *TTO* = time to onset, *TTR* = time to resolution, *tx* = treatment, *VAS* = visual analogue scale, *w/* = with, *w/o* = without

Head-to-Head Trials of LAIs Vs. LAIs

Paliperidone Palmitate Once-Monthly Vs. Paliperidone Palmitate 3-Monthly In two post hoc analyses of a 48-week, DBT (industry sponsor: Janssen) in 1016 relatively stable schizophrenia patients who were first stabilized in an open-label phase for 17 weeks on PP1M (50, 75, 100, or 150 mg) and then randomly assigned to PP3M (175, 263, 350, or 525 mg) (n = 512) or PP1M (50, 75, 100, or 150 mg) (n = 504) [49], injection site reactions and pain , measured using a clinician-rated 4-point scale (0 = absent; 1 = mild; 2 = moderate; 3 = severe) and a patient-rated visual analogue scale (VAS; 0 [no pain] to 100 [maximum pain]), were low and similar (7–13%) between the two treatments, regardless of injection site location and dose [64]. Mean (SD) VAS scores decreased from open-label baseline (22.0 [21.6]) to double-blind baseline (19.5 [20.6] vs. 18.4 [20.4]) and DB-endpoint (15.6 [17.9] vs. 15.5 [18.3]) [64] (Table 1). Furthermore, the overall incidence of spontaneously reported EPS-related treatment-emergent adverse events (TEAEs) decreased numerically from 12.6% (PP1M) in the open-label phase to 8.3% (PP3M) and 7.4% (PP1M) in the double-blind phase [65]. Among patients with reported EPS-related TEAEs, the median time to onset (TTO) for all EPS-related TEAEs was 17 days (PP1M) in the OL phase and 115 days (PP3M) and 98.5 days (PP1M) in the double-blind phase; median time to resolution (TTR) was 36.5 days (PP1M) in the open-label phase and 91 days (PP3M) and 85.5 days (PP1M) in the double-blind phase [65]. No dose- or age-related differences in TTO and TTR of EPS-related TEAEs were observed [65] (Table 4).

Aripiprazole Once-Monthly 400 mg Vs. Paliperidone Palmitate Once-Monthly In a post hoc analyses of a 28-week, ROLT (industry sponsor: Otsuka and Lundbeck) of 295 relatively stable schizophrenia patients, comparing AOM 400 mg (n = 148) with PP1M (flexible dosing 75–150 mg) (n = 147), each injected intramuscularly every 4 weeks [59], sexual dysfunction was significantly lower with AOM vs. PP1M (adjusted odds ratio [aOR] = 0.29 [95% CI = 0.14–0.61], p = 0.0012) in men (0.33 [0.13–0.86]; p = 0.023), women (0.14 [0.03–0.62]; p = 0.0099), and patients aged 18–35 years (0.04 [< 0.01–0.34]; p = 0.003) [66]. Further, prolactin concentrations decreased with AOM 400 (− 150.6 [274.4] mIU/L) and increased with PP1M (464.7 [867.5] mIU/L) [66] (Table 4).

All-Cause Discontinuation and Attitudes Toward and Acceptability of LAIs

Ten studies of LAIs (placebo-controlled: k = 3, OAP-controlled: k = 5, LAI–LAI comparisons: k = 2), of which four were post hoc analyses of a previously published primary study, investigated all-cause discontinuation, attitudes toward and acceptability of LAIs, in patients with

schizophrenia-spectrum disorders. Results regarding all-cause discontinuation, adherence, and treatment satisfaction are summarized by individual LAI and specific study comparator in Table 5.

Placebo-Controlled Trials of LAIs

RBP-7000 Vs. Placebo In an 8-week, DBPCT (industry sponsor: Indivior) of 337 patients with acute schizophrenia who were randomized to RBP-7000 90 mg (n = 111), RBP-7000 120 mg (n = 114), or placebo (n = 112), the discontinuation rate during the treatment period was somewhat higher for placebo (29.0%) than for RBP-7000 90 mg (22.4%), but compared to RBP-7000 120 mg (28.6%) [28•] (Table 5).

In a post hoc analysis of the same trial [28•], patient satisfaction, measured by the Medication Satisfaction Questionnaire (MSQ), improved significantly with RBP-7000 90 mg (p = 0.0009) and RBP-7000 120 mg (p = 0.0006) vs. placebo, with patients preferring RBP-7000 90 mg (p = 0.0001) as well as RBP-7000 120 mg (p = 0.0352) over placebo, as measured by the Preference of Medicine Questionnaire (POM) [53] (Table 5).

Aripiprazole Lauroxil Vs. Placebo In a post hoc analysis of a 12-week, DBPCT (industry sponsor: Alkermes) [33], focusing on a subgroup of patients with severe psychotic symptoms (baseline PANSS total score above the median score of 92 (n = 309)), who were randomly assigned to AL 441 mg (n = 207), AL 882 mg (n = 208), and placebo (n = 208)), the discontinuation rate during the treatment period was nearly twice as high for placebo (66%) than for AL 441 mg (37%) and for AL 882 mg (31%) [34] (Table 5).

Head-to-Head Trials of LAIs Vs. Oral Antipsychotics

Paliperidone Palmitate Once-Monthly Vs. Oral Antipsychotics In a 15-month, randomized, open-label trial (ROLT) (industry sponsor: Janssen) of 444 individuals with schizophrenia and a history of incarceration, comparing PP1M (flexible dosing 78–234 mg) (n = 226) with clinicians' choice OAPs (n = 218) [42], the discontinuation rates during the treatment period were comparable for PP1M (58.8%) and for OAPs (59.6%) as were adherence rates (PP1M = 100%, OAPs = 98.6%) [39] (Table 5). In subgroup analyses by OAP subgroups (COAPs, AOAPs, and risperidone/paliperidone), the discontinuation rate during the treatment period was 68.6% for COAPs (60.3% for PP1M), 73.3 for AOAPs (58.5% for PP1M), and 49.4% for risperidone/paliperidone (58.6% for PP1M) [43] (Table 5).

Risperidone Long-Acting Injection Vs. Atypical Oral Antipsychotics In an exploratory, independently funded, 2-year, ROLT of 85 early-phase (≤ 3 years of illness) schizophrenia-spectrum disorder patients who were first stabilized for 18 weeks on RLAI (25–50 mg) or AOAPs and then randomized to RLAI (25–50 mg) (n = 42) or AOAPs (n = 35), the discontinuation rate during the treatment period was comparable for RLAI (22.1%) and AOAPs (20.8%) [44] (Table 5).

Paliperidone Palmitate Once-Monthly vs. Oral Olanzapine In a 13-week, DBT funded by the Chinese government in 57 first-episode schizophrenia patients who were randomly assigned to PP1M (117, 156, or 234 mg) or oral olanzapine (5 mg), the discontinuation rate during the treatment period was similar for PP1M (45.6%) and olanzapine (43.9%) [45] (Table 5).

Paliperidone Palmitate Once-Monthly Vs. Paliperidone Extended-Release In a 24-week, ROLT funded by the Italian government of 72 patients with stable but symptomatic schizophrenia who were randomized to PP1M (flexible dosing 50–150 mg) (n = 36) or paliperidone extended-release (6–12/day) (n = 36), PP1M was superior to paliperidone extended-release in global treatment satisfaction (p = 0.001) and convenience (p = 0.037), measured by the Treatment Satisfaction Questionnaire for Medication (TSQM), as well as in service engagement (p = 0.001), measured by the Service Engagement Scale (SES) [46]. Furthermore, the discontinuation rate during the treatment period was only little less for PP1M (8.3%) than for paliperidone extended-release (11.1%) [46] (Table 5).

Head-to-Head Trials of LAIs Vs. LAIs

Paliperidone Palmitate Once-Monthly Vs. Paliperidone Palmitate 3-Monthly In a 48-week, DBT (industry sponsor: Janssen) of 1016 relatively stable schizophrenia patients who were first stabilized for 17 weeks on PP1M (50, 75, 100, or 150 mg) and then randomly assigned to PP3M (175, 263, 350, or 525 mg) (n = 512) or PP1M (50, 75, 100, or 150 mg) (n = 504), the discontinuation rate during the treatment period was roughly similar for PP1M (18%) and for PP3M (16.3%) [49] (Table 5).

Risperidone Long-Acting Injection Vs. Paliperidone Palmitate Once-Monthly In a 6-month, independently funded pilot ROLT of 30 patients with nonacute schizophrenia or SAD, comparing RLAI (n = 16) dosed flexibly up to 50 mg/2 weeks with PP (n = 14) dosed flexibly up to 150 mg/4 weeks, the discontinuation rate during the treatment period was only a little bit higher with RLAI (31.3%) than PP1M (28.6%) [60] (Table 5).

Meta-analyses of Randomized Controlled Trials of Long-Acting Injectable Antipsychotics in Schizophrenia

Altogether, five meta-analyses on RCTs of LAIs were published since 2016 [18, 20•, 21•, 25, 26].

Table 5 Randomized controlled trials of long-acting injectable antipsychotics: all-cause discontinuation/adherence/treatment satisfaction

Reference/design/country	Total *N*	Duration (weeks)	Population	Outcome	Age (years)	% male	% Hp at BL	Illness duration/age of onset	LAI/comparator	*N* per arm	Dose (mg)	All-cause discontinuation (%)/adherence (%)/treatment satisfaction
RBP-7000 vs. PBO *k* = 1, *n* = 337, age = 41.2, male = 77.5%												
Nasser et al., 2016 [28]/DBPCT/Isitt et al., 2016 [53]/post hoc analysis/USA	337	8	Acutely exacerbated SCZ w/ PANSS total of 80–120	*PANSS total*, CGI-S Post hoc: *Total AM plasma exposure*, PANSS total, CGI-S	41.2	76.5	N/Av	N/Av	RBP-7000 PBO	111 114 112	90 120	All-cause discontinuation: 90 mg 22.4, 120 mg 28.6, PBO 29 Subjects were significantly more satisfied w/ RBP-7000 vs. PBO (90 mg: $p = 0.0009$, 120 mg: $p = 0.0006$) and preferred (POM) RBP-7000 over their previous medication (90 mg: $p = 0.0001$, 120 mg: $p = 0.0619$)
AL vs. PBO *k* = 1, *n* = 309, age = 39.7, male = 69.0%												
Potkin et al., 2017 [34]/post hoc, subgroup analysis of DBPCT [Meltzer et al., 2015 [33]]/USA, Ukraine, Russia, Bulgaria, Romania, Philippines, Malaysia	309 (294 analyzed)	12	Acutely exacerbated SCZ w/ PANSS total above the median score of 92	*PANSS total*, PANSS subscales	39.7	69.0	100	N/Av	AL PBO	100 104 105	441 882	All-cause discontinuation: 441 mg 37, 882 mg 31, PBO 66
PP1M vs. OAP *k* = 2, *n* = 444, age = 38.2, male = 86.2%												
Alphs et al., 2016/post hoc analysis of ROLT [39], [Alphs et al., 2014 [42]]/USA	444	60	SCZ, taken into custody by the CJS ≥ 2 times in the previous 2 years w/ ≥ 1 leading to incarceration	*Mean number of tx failures (measured by MCF);* *Time to first tx failure (analysis based on age of onset);* *Time to first tx failure (analysis based on comorbid SA)*	38.2	86.3	N/Av	N/Av	PP1M OAPs: ARI, HAL, OLAN, PALI, PER, QUE, RIS	226 (130 w/ SA, 96 w/o SA, 42 ≤ 5 years, 183 > 5 years) 218 (134 w/ SA, 84 w/o SA, 35 ≤ 5 years, 182 > 5 years)	78–234 variable	All-cause discontinuation: PP1M 58.8, OAP 59.6 Adherence: PP1M 100, OAP 98.6
Kim et al., 2016 [43]/post hoc analysis of ROLT [Alphs et al., 2014 [42]]/USA	171 407 293	60	SCZ, taken into custody by the CJS ≥ 2 times in the previous 2 years w/ ≥ 1 leading to incarceration	*Time to first tx failure*	36.9 38.2 37.7	87.2 86.0 84.6	77% 79% 78%	22% ≤ 5 years 78% > 5 years 17% ≤ 5 years 83% > 5 years 18% ≤ 5 years 82% > 5 years	PP1M COAP (HAL, PER) PP1M AOAP (OLAN, ARI, QUE, PALI, RIS) PP1M RIS/PALI	136 35 224 183 208 85	78–234 variable 78–234 variable 78–234 variable	All-cause discontinuation: PP1M 60.3, COAP 68.6 PP1M 58.5, AOAP 73.3 PP1M 58.6, RIS/PALI 49.4

Table 5 (continued)

Reference/design/country	Total *N*	Duration (weeks)	Population	Outcome	Age (years)	% male	% Hp at BL	Illness duration/age of onset	LAI/comparator	*N* per arm	Dose (mg)	All-cause discontinuation (%)/adherence (%)/treatment satisfaction
RLAI vs. AOAP *k* = 1, *n* = 85, age = 22.7, male = 84.4%												
Malla et al., 2016 [44]/ROLT/Canada	85 (77 analyzed)	Stabilization on RLAI/AOAP 18 RCT 86	Early-phase SS w/ PANSS total score of 60–120	*Time to stabilization and relapse, PANSS total, positive, and negative, CGI-S*	22.7	84.4		N/Av	100% < 3 years	RLAI AOAP (QUE, OLAN, RIS)	42 35	25–50 300–500, 15–20, 1–6
All-cause discontinuation: RLAI 22.1, AOAP 20.8												
PP1M vs. olanzapine *k* = 1, *n* = 57, age = 22.7, male = 64.9%												
Huang et al., 2018 [45]/DBT/China	57	13	SCZ w/ PANSS total score of 60–120	*PANSS total*, PANSS subscales, metabolic assessments	22.7	64.9	100	100% < 1 year	PP1M Oral OLAN	28 29	117, 156, 234 5	All-cause discontinuation: PP1M 45.6, oral OLAN 43.9
PP1M vs. paliperidone extended-release *k* = 1, *n* = 72, age = 46.4, male = 43.1%												
Bozzatello et al., 2019 [46]/ROLT/Italy	72	24	Clinically stable SCZ w/ a change in CGI-S score of ≤ 1	CGI-S	46.4	43.1	0	N/Av	PP1M PALI ER	36 36	50–150 6–12/day	Sig. effects between subjects were found for the two domains "overall satisfaction" ($p = 0.001$) and "convenience" ($p = 0.037$) of the TSQM, and the SES ($p = 0.001$) All-cause discontinuation: PP1M 8.3, PALI ER 11.1
PP1M vs. PP3M *k* = 1, *n* = 1429, age = 38.7, male = 53.0												
Savitz et al., 2016 [49]/DBT/USA, EU, Japan, China, Russia	1429	Stabilization on PP1M 17 DBT 48	Clinically stable SCZ, PANSS total score < 70	*Relapse-free rates*, PANSS total score, PANSS subscale, Marder factor scores, CGI-S score	38.7	53.0	61	N/Av	PP1M PP3M	504 (157 w/ recent oral RIS/PALI) 512 (166 w/ recent oral RIS/PALI	50, 75, 100, or 150 175, 263, 350, or 525	All-cause discontinuation: PP1M 18.0, PP3M 16.3
RLAI vs. PP1M *k* = 1, *n* = 30, age = 45.0, male = 52.4%												
Koshikawa et al., 2016 [60]/ROLT/Japan	30 (21 analyzed)	24	Nonacute SCZ or SAD w/ PANSS total score ≤ 120	*SFS*, *BACS*	45.0	52.4	0	Mean age of onset 31.1	RLAI PP1M	16 14	Flexibly up to 50 mg/2 weeks	All-cause discontinuation: RLAI 31.3, PP1M 28.6

Table 5 (continued)

Reference/design/country	Total *N*	Duration (weeks)	Population	Outcome	Age (years)	% male	% Hp at BL	Illness duration/age of onset	LAI/comparator	*N* per arm	Dose (mg)	All-cause discontinuation (%)/adherence (%)/treatment satisfaction
											flexibly up to 150 mg/4 weeks	

AL = aripiprazole lauroxil, *AM* = active moiety, *AOAP* = atypical oral antipsychotics, *ARI* = aripiprazole, *BACS* = Brief Assessment of Cognition in Schizophrenia, *BL* = baseline, *CGI-S* = Clinical Global Impression-Severity, *CJS* = criminal justice system, *COAP* = conventional oral antipsychotic, *DB* = double-blind, *DBT* = double-blind trial, *DBPCT* = double-blind placebo-controlled trial, *HAL* = haloperidol, *HD* = haloperidol decanoate, *hp* = hospitalization, *LAI* = long-acting injectable, *N/Av* = not available, *MCF* = mean cumulative function, *OL* = open-label, *OLAN* = olanzapine, *PALI* = paliperidone, *PALI ER* = paliperidone extended-release, *PANSS* = Positive and Negative Syndrome Scale, *PBO* = placebo, *PER* = perphenazine, *PP1M* = paliperidone palmitate once-monthly, *PP3M* = paliperidone palmitate 3-monthly, *QUE* = quetiapine, *RIS* = risperidone, *RLAI* = risperidone long-acting injectable, *ROLT* = randomized open-label trial, *SA* = substance abuse, *SAD* = schizoaffective disorder, *SCZ* = schizophrenia, *SES* = Service Engagement Scale, *SFS* = Social Functioning Scale, *TSQM* = Treatment Satisfaction Questionnaire for Medication, *tx* = treatment, *w/* = with, *w/o* = without

In one meta-analysis funded by the National Evidence-based Healthcare Collaborating Agency, 17 RCTs of SGA-LAIs vs. SGA-OAPs were pooled (n = 6362) [18]. In the analyses of specific outcomes including only two to six RCTs, SGA-LAIs were associated with significantly lower relapse (RR = 0.85; 95% CI = 0.74–0.99), longer time to relapse ("SMD" = 0.42; 95% CI = 0.29–0.54), fewer hospital days (SMD = − 0.11; 95% CI = − 0.22 to − 0.01), and lower depression ratings (SMD = − 1.69; 95% CI = − 2.95 to − 0.43). Conversely, there were no significant differences in raw hospitalization rates (RR = 0.83; 95% CI = 0.62–1.11), remission (RR = 1.07; 95% CI = 0.99–1.15), psychopathology measured with PANSS (SMD = − 0.05; 95% CI = − 0.12 to 0.12) and CGI-S (SMD = − 0.05; 95% CI = − 0.13 to 0.04), and all-cause discontinuation (RR = 0.93; 95% CI = 0.82–1.05), but nonadherence also did not differ in the RCT population (RR = 0.58; 95% CI = 0.09–3.35). Moreover, although LAIs appeared to be associated with a greater reduction in EPS ratings (SMD = − 0.01; 95% CI = − 0.15 to 0.12), LAIs were also associated with a greater incidence of extrapyramidal syndrome (RR = 1.61; 95% CI = 1.27–2.04) and prolactin-related adverse effects (RR = 2.48; 95% CI = 1.60–3.84), at least in samples randomized to SGA-OAPs that were generally not matched for the specific LAI [18].

In contrast to these half positive, half neutral findings, another independently funded meta-analysis of 18 RCTs (n = 4796) pooled LAI data for the SGA-LAIs risperidone, olanzapine, and aripiprazole and the FGA-LAIs zuclopenthixol, fluphenazine, and haloperidol [25]. Analyzing each of the LAIs separately, all-cause discontinuation (primary outcome) did not differ significantly between the specific LAIs and compared group of OAPs, except for a small advantage for LAI aripiprazole (RCTs = 2, n = 986; RR = 0.78; 95% CI = 0.64–0.95). Similarly, each of the individual LAIs was not different from OAPs regarding intolerability-related discontinuation, extrapyramidal symptoms, prolactin increase (except for a small advantage for LAI risperidone: RR = 0.81, 95% CI = 0.68–0.98, NNT = 8), weight gain, nonresponse, relapse, and inefficacy-related discontinuation (except for a small disadvantage for LAI olanzapine 1.52; 95% CI 1.12 to 2.07, NNH = 20) [25].

Additionally, a small also independently funded meta-analysis of only five RCTs (n = 1022) investigated the comparative efficacy and safety of LAIs vs. OAPs in the important subgroup of patients with recent-onset psychotic disorders [20•]. In RCTs lasting on average 18.0 ± 7.6 months that compared paliperidone-LAI or risperidone-LAI with OAPs, no significant difference emerged between LAI and OAP treatment regarding relapse prevention (studies = 3, n = 875; RR = 0.67, 95% CI = 0.24–1.83). However, results were highly heterogeneous, with two studies showing significant superiority of the LAIs vs. OAPs, while one RCT showed no difference between LAIs and OAPs. Similarly, pooled

together, LAIs and OAPs did not differ significantly regarding the improvement in the PANSS total scores (studies = 2, n = 786, weighted mean differences = − 2.26, 95% CI = − 5.22 to 0.70), all-cause discontinuation (studies = 4, n = 920, RR = 0.90, 95% CI = 0.75–1.08), adverse events (studies = 2, n = 800, RR = 1.13, 95% CI = 1.03–1.25), and mortality (studies = 3, n = 883, RR = 1.03, 95% CI = 0.06–16.42). Nevertheless, LAIs outperformed OAPs regarding inefficacy-related discontinuation (RR = 0.34, NNT = − 50) and nonadherence-related discontinuation (RR = 0.30, NNT = − 33). Conversely, however, compared to mostly mixed and clinician's choice OAPs, LAIs were associated with a higher incidence of ≥ 1 adverse effect (RR = 1.13) and tremor (RR = 2.38) [20•].

Two independently funded meta-analyses focused exclusively on safety/tolerability. One of these two meta-analyses evaluated 16 RCTs (n = 4902) comparing LAIs and OAPs, including only LAI–OAP pairs of the same OAP (allowing oral risperidone and paliperidone as comparators for either risperidone or paliperidone LAI) [21•]. Out of all 119 reported adverse events, LAIs and OAPs did not differ significantly regarding 115 (96.6%) of them. LAIs were similar to OAPs regarding the frequency of intolerability-related all-cause discontinuation, serious adverse events, all-cause mortality, and mortality for reasons excluding accident or suicide. Compared to OAPs, LAIs were associated with significantly more akinesia, low-density lipoprotein cholesterol change, and anxiety, whereas LAIs were associated with significantly lower prolactin change and hyperprolactinemia [21•].

Finally, the second meta-analysis pooled data from 52 acute phase and maintenance/relapse prevention RCTs (n = 17,416) with a mean study duration of 28.9 weeks for LAIs vs. placebo and of 64.5 weeks for LAIs vs. OAPs [26]. In these analyses, neither pooled together (nor individual LAIs, i.e., aripiprazole, fluphenazine, olanzapine, paliperidone, and risperidone) differed significantly from placebo regarding all-cause mortality (RR = 0.64, p = 0.37) or suicide-related mortality (RR = 0.98, p = 0.98). Similarly, neither pooled LAIs (nor individual LAIs, i.e., aripiprazole, fluphenazine, haloperidol, olanzapine, paliperidone, risperidone, and zuclopenthixol) differed from pooled OAPs regarding all-cause mortality (RR = 0.71, p = 0.30) and suicide-related mortality (RR = 0.94, p = 0.91) [26].

Conclusion

This targeted systematic review of 31 RCTs (n = 4738) of LAIs published between January 2016 and March 2019 (vs. placebo: k = 11, vs. OAPs: k = 7, vs. another LAI: k = 13) summarized recent findings of 7 original RCTs and 24 post hoc analyses of previously published primary RCTs. These trials reported results on (i) novel long-acting injectable formulations, (ii) efficacy of LAIs for symptom improvement and prevention of relapse and hospitalization, (iii) efficacy of LAIs on functionality and quality of life, (iv) tolerability and safety of LAIs, and (v) attitudes toward and acceptability of LAIs.

Regarding novel LAI formulations, RCTs reported that RBP-7000 (Perseris™ risperidone) was superior to placebo in symptom improvement, and aripiprazole lauroxil nanocrystal dispersion (AL_{NCD}; Aristada Initio™) enabled faster achievement of aripiprazole plasma concentrations with minimized oral supplementation to the first day of administration compared to the previously approved 21-day oral supplementation regimen.

Regarding total symptom improvement, LAIs were superior to placebo and equally effective compared to OAPs, at least in patients selected to agree to double-blind placebo-controlled trials of LAIs [14], while one study demonstrated favorable results for PP1M in the improvement of negative symptoms [46], but ratings were only based on an adapted CGI-S assessment, and no differences were found in LAI–LAI comparisons. For preventing relapse and hospitalization, which are outcomes of key interest [10–12], LAIs were superior to placebo, and as effective as OAPs using RLAI in early-phase (≤ 3 years of illness) schizophrenia-spectrum disorder patients, while there was one study favoring PP1M over OAPs [42], even with reduced statistical power (COAP, AOAP, oral risperidone/paliperidone), with a numerically greater advantage in recent-onset schizophrenia patients, while in LAI–LAI comparisons, HD demonstrated greater efficacy in preventing relapse and hospitalization in younger patients (18–45 years), yet PP1M and PP3M were comparably effective in a big sample of schizophrenia patients.

For improving functioning, LAIs were superior to placebo, with the newly approved RBP-7000 being superior to improving functioning as well as quality of life, while PP1M is as effective as OAPs in improving functioning and quality of life, and in LAI–LAI comparisons, PP1M and PP3M showed comparable results, AOM was superior to PP1M (in unblinded assessments), and PP1M was superior to RLAI.

Moreover, LAIs were noninferior to placebo regarding tolerability and safety using AL, and comparable to AOAPs using RLAI, with favorable results reported for the partial D2 agonist AOM vs. the full D2 antagonist PP1M in terms of sexual functioning, and with comparable results for PP1M and PP3M regarding injection site reactions and pain.

Furthermore, compared to placebo, LAIs were associated with less all-cause discontinuation, but at least in the controlled setting of RCTs, there were little, if any differences in all-cause discontinuation between LAIs and OAPs. In contrast, compared to placebo as well as OAPs, LAIs enhanced patient satisfaction (RBP-7000, PP1M). Furthermore, compared to OAPs alone, LAIs also enhanced service engagement (PP1M) and were preferred (RBP-7000) by patients, implying that the current underutilization in clinical practice may be due

to lack of familiarity or enthusiasm of many clinicians [13, 67•]. However, since current data are still limited, more information on patients' as well as clinicians' attitudes toward LAIs are needed to draw further conclusions.

Finally, results of meta-analyses of LAIs vs. OAPs have yielded mixed results including significant advantages regarding some efficacy and effectiveness outcomes for LAIs or neutral results, but without any of the outcomes favoring OAPs. In terms of adverse effects, some isolated adverse effects seemed to favor OAPs, yet findings were likely biased by differences in the LAI arm (fixed to one LAI) and OAP arm (mixed, with choice being made adjusting for prior experiences, including past adverse effect patterns). When comparing the same antipsychotic in LAI or OAP formulation, adverse effects appeared similar in 97% of the reported adverse effects, and two meta-analyses reported that mortality rates were not higher with LAIs vs. OAPs, both in short-term, acute as well as in longer-term maintenance/relapse prevention studies. However, as discussed before [14, 68], RCTs that exclude a large number of patients and that may instead differentially include those with greater illness insight, adherence, and stability may not be the best (and for sure should not be the only) way to evaluate the real-world efficacy and effectiveness of LAIs vs. OAPs, and studies with other designs, namely mirror-image and cohort studies, also need to be considered.

Limitations of this selected review are inherent to its design, i.e., the restriction to the evidence published from January 2016 to March 2019, performed in order to provide an update to the comprehensive publication on this topic published in 2016 [13], and the restriction to RCTs, which—although being considered a gold standard design in medicine—are relatively rare, have small sample sizes and bias samples toward patients with lower illness severity, greater illness insight and adherence, and generally smaller sample sizes and shorter follow-up durations that did not allow analysis of impotent outcomes such as for example all-cause and specific-cause mortality [69••, 70••, 71], or rare/long-term adverse effects, such as tardive dyskinesia [72] or diabetes mellitus, myocardial infarction, or stroke [73–75]. To address the impact of LAIs vs. OAPs, the complementary analysis of cohort studies and, especially, nationwide database studies can be helpful.

Nevertheless, despite these limitations, the review of LAI studies in people with schizophrenia-spectrum disorders published over the 3-year period of this review confirmed prior results [10, 13, 76] that LAIs are superior to placebo in all areas studied, but further research is needed to identify a clear advantage of LAIs vs. OAPs as well as patient and treatment characteristics moderating and mediating such potential advantages, and to allow more accurate differentiation between different LAI formulations. It should be noted that in the areas studied, LAIs were largely comparable to OAPs, while they sometimes showed better results than OAPs, but never worse results than OAPs. Moreover, as stated above, the population agreeing to be included in blinded and open RCTs may not be fully representative of clinically treated populations, which is why examination of data in other, complementary study designs (mirror image and cohort studies) is also important [13, 14]. Taken together, this review demonstrated that LAIs are an effective treatment option for both early-phase/first-episode and more chronic schizophrenia-spectrum disorders.

As summarized in recent expert consensus reports also published within the 3-year period of this review [13, 77, 78], specific patient and medication characteristics should be considered when identifying appropriate clinical situations for the use of LAIs, choosing, initiating, switching to, and optimizing LAI treatment in patients with schizophrenia eligible for LAIs. These efforts should include the systematic management of breakthrough psychosis [79] and provision of adequate and impactful education and training [67•] regarding LAI use in usual care settings. For example, a recent study demonstrated in a cluster-randomized study design that after training the entire treatment team dealing with first-episode and early-phase (≤ 5 years of illness) schizophrenia patients assigned to sites regularly offering LAIs as standard of care, 76% of the total sample and 91% of those agreeing to be part of the open-label study had at least one LAI treatment within 3 months of joining the treatment service [79•]. These data are in stark contrast to clinicians reporting that 80% of their patients refuse the use of LAIs [80] Since patients and families are not encountering barriers externally but these barriers are within themselves internally greater than those encountered in patients and families [81, 82] and that adequate training and education could improve the provision of assured maintenance treatment in schizophrenia, which is clearly a goal for improving outcomes [9, 83•, 84].

Compliance with Ethical Standards

Conflict of Interest Luisa Peters, Amanda Krogmann, Laura von Hardenberg, Katja Bödeker, and Viktor B. Nöhles each declare no potential conflicts of interest. Christoph U. Correll has been a consultant and/or advisor to or has received honoraria from: Alkermes, Allergan, Angelini, Boehringer-Ingelheim, Gedeon Richter, Gerson Lehrman Group, Indivior, IntraCellular Therapies, Janssen/J&J, LB Pharma, Lundbeck, MedAvante-ProPhase, Medscape, Merck, Neurocrine, Noven, Otsuka, Pfizer, Recordati, Rovi, Servier, Sumitomo Dainippon, Sunovion, Supernus, Takeda, and Teva. He has provided expert testimony for Bristol-Myers Squibb, Janssen, and Otsuka. He served on a Data Safety Monitoring Board for Boehringer-Ingelheim, Lundbeck, Rovi, Supernus, and Teva. He received royalties from UpToDate and grant support from Janssen and Takeda. He is also a shareholder of LB Pharma.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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